Medicinrådet

Bilag til Medicinrådets vurdering af givinostat til behandling af Duchennes muskeldystrofi

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. givinostat
2. Forhandlingsnotat fra Amgros vedr. givinostat
3. Ansøgers endelige ansøgning vedr. givinostat

9 juni 2026

Høringssvar fra Italfarmaco til Medicinrådet vedrørende rapporten for Duvyzat ® (givinostat) til behandling af Duchennes Muskeldystrofi (DMD) hos ambulante patienter i alderen 6 år og ældre, som er i samtidig behandling med kortikosteroider

Italfarmaco (ITF) takker for muligheden for at kommentere på den rapport som vi har modtaget 22 maj 2026 inden der tages en endelig beslutning i DMC 24 juni. Vi anerkender det store arbejde som sekretariat og fagudvalget har udført, men mener der er pointer, som bør yderligere inddrages for at kunne vurdere den reelle værdi af behandlingen for patienter med Duchennes Muskeldystrofi (DMD) i Danmark.

Stort medicinsk behov, hvilket bør understøttes af alvorlighedsprincippet

Duchennes muskel dystrofi (DMD) er en sjælden genetisk alvorlig, progressiv og dødelig neuromuskulær lidelse, der er karakteriseret ved irreversibelt muskeltab og nedsat muskelregenerering, hvilket resulterer i tab af gang funktion, respiratoriske og kardiologiske komplikationer og for tidlig død. De fleste patienter mister evne til at gå omkring 11-13-årsalderen og har behov for kørestol (Isohanni et al. 2026, Annexstad et al. 2019). Data for dødelighed er blevet omfattende dokumenteret og for nyligt dokumenteret i et dansk studie som indikerer en gennemsnitlig overlevelsesalder for drenge og unge mænd med DMD 26.8 år (IQR: 19–34) (Rudolfsen et al. 2024). Trods årtiers forskning er glukokortikoider (GC'er) fortsat den eneste nuværende behandling, der anvendes i EU, hvilket understreger det presserende behov for effektive sygdomsmodificerende behandlinger. Der er aktuelt ingen DMD produkter under vurdering hos EMA.

Duvyzat® (givinostat) er den første sygdomsmodificerende behandling, der har vist statistisk signifikant effekt på det primære endepunkt ift sygdomsprogression og er godkendt i Europa. De sekundære endepunkter peger konsekvent i samme retning som det primære endepunkt og særligt ift skanning af fedt fraktion i lårmusklerne.

Opfølgningsstudiet OLE viste en forsinkelse i tiden til tab af gangfunktion sammenlignet med en historisk kontrolgruppe: HZ ratio: 0,201 (SE 0.142; 0.285), svarende til en forskel på 17.97 år mod 12.28 år (NICE 2026a). En tilsvarende effekt på andre sygdomsmilepæle, såsom nedsat respiratorisk funktion, forventes i takt med, at flere data bliver tilgængelige, på baggrund af givinostats virkningsmekanisme i muskelvævet.

Denne forsinkelse i sygdomsprogressionen kan bidrage til, at patienter med DMD bevarer deres selvstændighed længere og kan forbedre livskvaliteten for både patienter og pårørende.

Værdien af effekten for pårørende bør inkluderes

Når et barn får en sjælden diagnose som DMD, påvirker sygdommen hele familien – herunder forældre, søskende og bedsteforældre. Konsekvenserne for patienten kan derfor ikke adskilles fra de belastninger, sygdommen medfører for familien som helhed, både hvad angår omkostninger, livsvilkår og mental trivsel.

Mere end 50 % af forældrene til drenge og unge mænd med DMD oplever helbredsproblemer som følge af den belastning, deres barns sygdom medfører, og dette fører ofte til behov for medicinsk behandling (Schreiber-Katz et al. 2014). Belastningen skyldes både de omfattende praktiske opgaver, der følger med at have et alvorligt sygt barn, og de mentale udfordringer, der er forbundet med viden om sygdommens progressive karakter, det stigende plejebehov og barnets forventeligt tidlige død.

Desuden angav 60 % af forældrene, at deres karrieremuligheder var begrænsede, mens 49 % rapporterede reduceret livsindkomst som følge af deres søns sygdom, blandt andet på grund af nedsat arbejdstid eller ophør af beskæftigelse (Schreiber-Katz et al. 2014).

DMD medfører således et betydeligt økonomisk pres for de berørte familier. Dette påvirker både produktivitet, beskæftigelsesstatus og andre centrale livsområder, og byrden stiger i takt med sygdommens progression (Porteous et al. 2021). Det samme gælder de indirekte omkostninger, der er forbundet med familiens omsorgsansvar (Porteous et al. 2021).

Der er derfor tale om betydelige omkostninger for både familierne og samfundet, som ikke kan indregnes i den nuværende model struktur. Både SMC og NICE har anerkendt behovet for at inddrage pårørendebyrden og har derfor accepteret dette i deres sundhedsøkonomiske vurderinger (NICE 2026b) og begge har godkendt Duvyzat® (givinostat) til behandling af DMD i Storbritannien.

ITF mener på denne baggrund, at pårørendeperspektivet bør indgå i den endelige beslutning, selv om det endnu ikke er anerkendt i den nuværende sundhedsøkonomiske model.

Relevansen af valg af UK data for ekstern komparator arm

Som sjælden sygdom er der sparsom data for DMD, men North Star (NS) database (Muscular Dystrophy UK 2025) i UK har indsamlet data systematisk gennem årtier og har dannet grundlag for de internationale guidelines (Birnkrant et al. 2018a, Birnkrant et al. 2018b, Birnkrant et al. 2018c). NS data har både de respiratoriske sygdomsmilepæle samt data for tidligere sygdomsforløb og behandling og kunne derfor retrospektivt matches med patienterne i EPIDYS studiet, så de er sammenlignelige i alder og sygdomsforløb. Data derfra er desuden svarende hvad der ses i Norden (valideret af danske og nordiske læger) med fx tab af gangfunktion (LoA) omkring 12 år og tilsvarende til andre kilder (Annexstad et al. 2019, Isohanni et al. 2026). DK og UK følger de samme internationale guidelines for behandling og opfølgning af sygdomsmilepæle.

Overestimeret patient antal

ITF er overordnet enig med DMC i antallet af relevante patienter, men mener at optaget i rapporten er urealistisk baseret på erfaring fra andre lande og særligt fordi de danske klinikker endnu ikke har erfaring med Duvyzat® (givinostat). Samtidig forventes det ikke at alle patienter vil starte i behandling dels pga kliniske studier og dels da nogle patienter ikke kan tåle GC's og derfor ikke vil være relevante for behandling med Duvyzat®(givinostat). Dermed er både det prevalente og det incidente patient antal for højt i rapporten.

Herudover antager DMC fuld-års behandling for alle patienter i BIM, hvilket overestimerer budget impact signifikant, da diagnose og behandling i praksis vil ske løbende som følge af diagnose og patient alder.

ITF vil derfor opfordre til, at BIM opdateres ift et mere realistisk patientoptag.

Venlig hilsen

ITALFARMACO SpA, Rare Disease Nordics

Katja Lundberg Rand

Value, Access & governmental affairs director
Italfarmaco Cluster Nordics

Kristina Grafström

Head of rare Disease
Cluster Nordics, France & Benelux

References

Annexstad, E. J., Fagerheim, T., Holm, I., et al. 2019. Molecular and Clinical Characteristics of a National Cohort of Paediatric Duchenne Muscular Dystrophy Patients in Norway. J Neuromuscul Dis, 6, 349-359.

Birnkrant, D. J., Bushby, K., Bann, C. M., et al. 2018a. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management. Lancet Neurol, 17, 251-267.

Birnkrant, D. J., Bushby, K., Bann, C. M., et al. 2018b. Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bone health, and orthopaedic management. Lancet Neurol, 17, 347-361.

Birnkrant, D. J., Bushby, K., Bann, C. M., et al. 2018c. Diagnosis and management of Duchenne muscular dystrophy, part 3: primary care, emergency management, psychosocial care, and transitions of care across the lifespan. Lancet Neurol, 17, 445-455.

Isohanni, P., Auranen, M., Vesikansa, A., et al. 2026. Epidemiology, treatment practices, and societal and economic burden of Duchenne muscular dystrophy in Finland: A retrospective register and chart review study. J Neurol Sci, 485, 125903.

Muscular Dystrophy UK. 2025. Northstar programme [Online]. Available: https://www.musculardystrophyuk.org/research/current-projects/northstar-programme/ [Accessed 6 March 2025].

NICE. 2026a. Givinostat for treating Duchenne muscular dystrophy in people 6 years and over (TA1157) [Online]. Available: https://www.nice.org.uk/guidance/ta1157/resources/givinostat-for-treating-duchenne-muscular-dystrophy-in-people-6-years-and-over-pdf-2973530697447877 [Accessed 08 June 2026].

NICE. 2026b. NICE approves Duchenne muscular dystrophy treatment givinostat after commercial deal sealed [Online]. Available: https://www.nice.org.uk/news/articles/nice-approves-duchenne-muscular-dystrophy-treatment-givinostat-after-commercial-deal-sealed [Accessed 27 May 2026].

Porteous, D., Davies, B., English, C., et al. 2021. An Integrative Review Exploring Psycho-Social Impacts and Therapeutic Interventions for Parent Caregivers of Young People Living with Duchenne's Muscular Dystrophy. Children (Basel), 8.

Rudolfsen, J. H., Vissing, J., Werlauff, U., et al. 2024. Burden of Disease of Duchenne Muscular Dystrophy in Denmark - A National Register-Based Study of Individuals with Duchenne Muscular Dystrophy and their Closest Relatives. J Neuromuscul Dis.

Schreiber-Katz, O., Klug, C., Thiele, S., et al. 2014. Comparative cost of illness analysis and assessment of health care burden of Duchenne and Becker muscular dystrophies in Germany. Orphanet J Rare Dis, 9, 210.

Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

24.06.26

MBA/DBS

Forhandlingsnotat

Dato for behandling i Medicinrådet	24.06.2026
Leverandør	Italfarmaco SpA
Lægemiddel	Duvyzat (givinostat)
Ansøgt indikation	Behandling af Duchennes muskeldystrofi hos ambulante patienter ≥ 6 år
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende betingede priser på Duvyzat (givinostat):

Tabel 1: Forhandlingsresultat – betinget af Medicinrådets anbefaling

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Tilbud 1 SAIP (DKK)	Tilbud 2 SAIP (DKK)	Tilbud 3 SAIP (DKK)
Duvyzat	8,86 mg/ml, 140 ml	122.995,00	[redacted]	[redacted]	[redacted]
Forhandlet rabat ift. AIP			[redacted]	[redacted]	[redacted]

Tilbud 1: Betinget, flad rabat
Tilbud 2: Betinget, flad rabat + alternativ aftale (stop kriterium)
Tilbud 3: Betinget, flad rabat + alternativ aftale (forbrugsloft)

Priserne i tabel 1 er betinget af Medicinrådets anbefaling. Det betyder, at hvis Medicinrådet ikke anbefaler Duvyzat, indkøbes lægemidlet til den SAIP, der er angivet i tabel 2.

Tabel 2: Forhandlingsresultat – ikke betinget af Medicinrådets anbefaling

Lægemiddel	Styrke (pakning)	AIP (DKK)	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Duvyzat	8,86 mg/ml, 140 ml	122.995,00	[redacted]	[redacted]

Aftaleforhold

Amgros vil indgå en aftale på Duvyzat, som gælder fra den 01.07.2026 til den 31.03.2028 med mulighed for at forlænge 2x12 måneder. Leverandøren har mulighed for at sætte prisen ned i hele aftaleperioden.

[redacted]

Informationer fra forhandlingen

[redacted]

Konkurrencesituationen

I Medicinrådets vurderingsrapport sammenlignes Duvyzat med prednisolon og deflazacort. Tabel 3 viser de årlige lægemiddeludgifter for henholdsvis Duvyzat, prenisolon samt deflazacort.

Tabel 3: Sammenligning af lægemiddeludgifter pr. patient

Lægemiddel	Styrke (pakningsstørrelse)	Dosering*	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Duvyzat	8,86 mg/ml, 140 ml oral suspension	22,2 mg – 53,2 mg * 2 dagligt	[redacted]	For patient på 30 kg: [redacted] For patient på 60 kg: [redacted]
Prednisolon "DAK"	25 mg (100 stk. tabletter)	0,75 mg/kg/dag	[redacted]	For patient på 30 kg: [redacted] For patient på 60 kg: [redacted]
Deflazacort "Nordic Prime"	6 mg (60 stk. tabletter)	0,90 mg/kg/dag	[redacted]	For patient på 30 kg: [redacted] For patient på 60 kg: [redacted]

*Doseringen følger Medicinrådets vurderingsrapport tabel 2 side 16.

Status fra andre lande

Tabel 2: Status fra andre lande

Land	Status	Link
Norge	Under vurdering	Link til vurdering
England	Anbefalet	Link til anbefaling
Sverige	Under vurdering	

Opsummering

Der er forhandlet tre betingede tilbud med forskellige modeller for enten flad rabat, behandlingsstop ved sygdomsmilepæl eller loft over forbruget, samt et ubetinget pristilbud som er uafhængig af Medicinrådets anbefaling. Anbefales Duvyzat med en alternativ aftalemodel kræves der yderligere konkretisering før implementering af aftalen.

Medicinrådet

Instructions for companies

This is the template for submitting evidence to the Danish Medicines Council (DMC) as part of the appraisal process for a new medicinal product or a new indication for an existing medicine. The template is not exhaustive.

Please note the following requirements:

- When preparing their application, companies must adhere to the current version of the DMC's methods guide.
- Always use the current (latest updated) version of this template downloaded from the DMC's website.
- Headings, subheadings and appendices must not be removed. Tables must not be deleted or edited, unless it is explicitly stated in the text.
- Text in grey and [in brackets] is only for example purposes and must be deleted.
- All sections in the template must be filled in. If a section or an appendix is not applicable, state "not applicable" (N/A) and explain why.
- The main body of the application must not be longer than 100 pages (including the title page, contact information and references – excluding appendices).
- The formatting is not to be altered and all cross-references must work.
- All applications must comply with the general data protection regulations, find more information on DMC's data policy here.
- Submissions in either Danish or English are accepted.

The assessment process cannot be initiated before all the requirements are met.

Documentation to be submitted

The following documentation must be sent to the DMC's email medicinraadet@medicinraadet.dk:

- Application in word format*
- Application in PDF format*
- Health economic model including budget impact model in one Excel file, with full access to the programming code. The model must include relevant sheets from the DMC Excel template 'Key figures including general mortality' available on the DMC's website.
- The European Public Assessment Report (EPAR) should be submitted. Send a draft version if the final one is not published at the time of submission, and send the final version as soon as possible.

Confidential information and blinding

The Danish Medicine Council publishes the application (including attachments) on the website together with the recommendation.

The applicant has the option to blind any confidential information in the application incl. appendices.

Medicinrådet

The application and paper/appendices

If there is confidential information in the application or note/appendices, the company must submit two versions of both the application and note/appendices:

- a version for the DMC's case processing, where the confidential information is marked with yellow marking.
- a version for publication on the DMC's website, where the confidential information is blinded with black marking. The DMC publishes this version.

It is the pharmaceutical companies that must ensure that the blinding is sufficient, so that the confidential information cannot be read when the document is edited.

Therefore, the applicant must ensure that the confidential information is sufficiently redacted blinded for publication on the DMC's website. This can be done, for example, by covering the text/information to be redacted with a black marker simultaneously replacing the underlying text with crosses ("XXX"), so that the text/information cannot be read when editing the document.

Read about redaction of confidential information on the DMC's website.

About macros in Excel

Due to IT security requirements, Excel files containing macros must be authorized and signed by the applicant before being submitted to the DMC. Find more information here.

Application for the assessment of Duvyzat (givinostat) for the treatment of Duchenne Muscular Dystrophy

Contact information

Contact information	
Name	**Katja Lundberg Rand**
Title	Value, access and government affairs director
Phone number	+45 27211072
E-mail	k.rand@italfarmacogroup.com
Name	**Kristina Grafström**
Title	General Manager, Rare disease Italfarmaco Nordics
Phone number	+46 70 523 05 96
E-mail	k.grafstrom@italfarmacogroup.com

[If a company wishes to use external representation in relation to the application for evaluation of a new medicine / extension of indications, the following power of attorney must be completed and sent to medicinraadet@medicinraadet.dk.]

Color scheme for text highlighting	
Color of highlighted text	**Definition of highlighted text**
	Confidential information
[Other]	**[Definition of color-code]**

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Tables and Figures

Abbreviations

Abbreviation	Definition	Abbreviation	Definition
4SC	4-stair climb	LLN	Lower Limit Normal
6MWT	6-minute walking test	LS	Least square
10MWR	10-metre walk/run	LTBP4	latent transforming growth factor β-binding protein 4
10MWT	10-metre walking test	LV	Left ventricular
AAV	Adeno-associated virus	LVEF	Left ventricular ejection fraction
ACEis	ACE inhibitors	LYs	Life years
ACR	Adjusted cost ratio	M	Million
ADHD	Attention-deficit/hyperactivity disorder	MA	Marketing Authorization
ADP	Ambulatory declined phase	MAH	Marketing Authorization Holder
AE	Adverse event	MAIC	Matching-adjusted indirect comparison
AESI	adverse event of special interest	MCID	Minimal clinically important difference
AFT	acceleration factor	MDC	Minimal detectable change
AIC	Akaike information criterion	MedDRA	Medical Dictionary for Competent Activities
ALT	Alanine aminotransferase	MFAF	Muscle fibre area fraction
ANCOVA	Analysis of covariance	MFF	Muscle fat fraction
ANSM	National Agency for the Safety of Drugs and Healthcare Products	MFM	Motor function measure
ASD	Autism spectrum disorder	MHC	Major histocompatibility complex
ASO	Antisense oligonucleotide	miRNA	MicroRNA
AST	Aspartate aminotransferase	MLPA	Multiplex ligation-dependent probe amplification
ATC	Anatomical Therapeutic Chemical	MoA	Mechanism of action
AUC	Under the curve	MPC	Muscle progenitor cell
AUCO-24	Area under the concentration-time curve during 24 h	MR	Magnetic resonance
ARB	Angiotensin II receptor blockers	MRI	Magnetic resonance imaging
BID	Twice daily	mRNA	Messenger ribonucleic acid
ß-AR	beta-adrenergic receptor blockers	MRS	Magnetic resonance spectroscopy
BIA	Budget impact analysis	MuSC	Muscle stem cell
BIC	Bayes information criterion	MyoD	Myoblast determination protein 1
Bid	Twice daily	n	number of patients in the study population
BL	Baseline	N/A	Not applicable
BMD	Becker Muscular Dystrophy	NDA	New Drug Application
BMI	Body mass index	NE	Not estimable
BOI	Burden of illness	NH	Natural history
Cmax	Maximum concentration	NHM	Natural history model
CDC	Centers for Disease Control and Prevention	NICE	National Institute for Health and Care Excellence
CDCs	Cardio-sphere-derived cells	NIV	Non-invasive ventilation
CEA	Cost-effectiveness analysis	nmDMD	nonsense mutation DMD
CEM	cost-effectiveness model	NO	Nitrous oxide

CEPS	Economic Committee for Health Products	NOK	Norwegian Krone
CFB	Change from baseline	NOS	Nitrous oxide synthase
CHMP	Committee for Medicinal Products for Human Use	NR	Not reported
CI	Confidence interval	NSAA	North Star Ambulatory Assessment
CINRG	Cooperative International Neuromuscular Research Group	OATP	Organic anion transporting polypeptide
CK	Creatine kinase	OCT2	Organic cation transporter 2
CMR	Cardiovascular MRI	OLE	Open-label extension
CNS	Central nervous system	P-gp	P-glycoprotein
COI	Cost of illness	PD	Pharmacodynamics
COMP	Committee for Orphan Medicinal Products	PDUFA	Prescription Drug User Fee Act
CPRD	Clinical Practice Research Datalink	PedsQL	Pediatric Quality of Life Inventory TM 4.0
CSA	Cross-sectional area	PEF	Peak exploratory flow
CRF	Case report form	PetCO2	Partial Pressure of End-Tidal Carbon Dioxide
DAPC	Dystrophin-associated protein complex	PFT	Pulmonary function test
DCO	Data cut-off	PH	Project HERCULES
DDI	Drug-drug interaction	PK	Pharmacokinetics
DG	Dystroglycan	PNDS	Protocole national de diagnostic et de soins
DGC	Dystrophin-glycoprotein complex	PODCI	Pediatric Outcome Data Collection Instrument
DKK	Danish crown	PT	Preferred term
DMD	Duchenne Muscular Dystrophy	PTC	Premature termination codon
ECG	Electrocardiogram	PUL	Performance of the Upper Limb
ECHO	echocardiogram	QALY	Quality adjusted life year
EK	Egen Klassifikation	QoL	Quality of life
EMA	European Medicines Agency	QTc	Corrected QT interval
EoS	End of study	RCT	Randomised controlled trial
ESS	Effective sample size	RDI	Relative dose intensity
EQ-5D-3L	European Quality of Life 5 Dimension Questionnaire – 3 Level Version	RNA	Ribonucleic acid
EQ-5D-3L	European Quality of Life 5 Dimension Questionnaire – 5 Level Version	ROM	Range of motion
EU	European Union	ROS	Reactive oxygen species
FAP	Fibro-adipogenic progenitor	S	Screening
FDA	Food and Drug Administration	SAE	Serious adverse event
FEV1	Forced expiratory volume in 1 second	SAS	Safety analysis set
FF	Fat fraction	SC	Stair climb
FVC	Forced vital capacity	SCG	Sarcoglycan
FVC%p	forced vital capacity percent predicted for age	SD	Standard deviation
FY	Financial year	SE	Standard error
GGT	gamma glutamyl transpeptidase	SEC	Second

GI	Gastrointestinal	SEM	Standard error of measurement
GIOP	Glucocorticoid-induced osteoporosis	SF-12	Short Form-12 Health Survey
GLS	Generalised least square	SF-36	Short Form-36 Health Survey
GC	glucocorticoid	SI	Système International
H2O	Water	SLR	systematic literature review
HDAC	Histone deacetylase	SmPC	summary of product characteristics
HDACi	Histone deacetylase inhibitor	SoC	Standard of care
HES	Hospital Episode Statistics	STA	Single Technology Assessment
HFI	Hereditary fructose intolerance	TEAE	Treatment-emergent adverse event
HHM	Hand-held myometer	TFT	Timed function test
HIV	human immunodeficiency virus	TG	Triglyceride
HR	Hazard ratio	TGF-β	Transforming growth factor-beta
HRQoL	Health-related quality of life	TNF	Transforming growth factor
HS	Health state	TNF-α	Tumour necrosis factor-alpha
HTMF	hand-to-mouth function	TTO	Time trade off
HUI	Health Utilities Index	TTR	Time to rise from floor
ICF-CY	International Classification of Functioning, Disability, and Health-Children and Youth Version	UK	United Kingdom
IDMC	Independent Data Monitoring Committee	ULN	Upper limit normal
IMCT	Intramuscular connective tissue	US	United States
IMP	Investigational medicinal product	VAS	Visual analogue scale
ICER	Incremental cost-effectiveness ratio	VAT	Value added tax
ISE	Integrated summary of efficacy	VL	Vastus lateralis
IQR	Interquartile range	VL MFF	Vastus lateralis muscle fat fraction
ITT	Intention-to-treat	VLFF	Vastus Lateralis Fat Fraction.
KM	Kaplan-Meier	WHO	World Health Organization
LDH	Lactate dehydrogenase	WTP	Willingness-to-pay
LoA	Loss of Ambulation		

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Duvyzat
Generic name	Givinostat
Therapeutic indication as defined by EMA	Duvyzat is indicated for the treatment of Duchenne muscular dystrophy (DMD) in ambulant patients, aged 6 years and older, and with concomitant corticosteroid treatment
Marketing authorization holder in Denmark	Italfarmaco SpA (MAH), Campuspharma AB, org nr 556534-0287 (Local representative)
ATC code	M09AX14
Combination therapy and/or co-medication	Givinostat should be given with concomitant corticosteroids

Overview of the medicine	
(Expected) Date of EC approval	30th of June 2025
Has the medicine received a conditional marketing authorization?	Yes
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	4 July 2012, orphan designation (EU/3/12/1009)
Other therapeutic indications approved by EMA	No
Other indications that have been evaluated by the DMC (yes/no)	No
Joint Nordic assessment (JNHB)	Are the current treatment practices similar across the Nordic countries (DK, FI, IS, NO, SE)? Yes Is the product suitable for a joint Nordic assessment? No If no, why not? Givinostat is not a hospital product in all Nordic countries
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	Bottle of 140 mL of givinostat 8.86 mg/mL oral suspension with a 5 mL graduated dosing syringe

2. Summary table

Summary	
Indication relevant for the assessment	Duchenne muscular dystrophy (DMD) in ambulant patients, aged 6 years and older, and with concomitant corticosteroid treatment
Dosage regiment and administration	Twice daily orally, following a weight-based scheme (2.5 ml at lowest weight ≥15 kg, and 6.0 ml at highest weight ≥60 kg
Choice of comparator	Prednisone (20.47% of patients) and deflazacort (79.53% of patients)
Prognosis with current treatment (comparator)	DMD is characterised by early progressive and irreversible muscle degeneration injury of all muscles throughout the body from birth, ultimately resulting in the loss of ambulation around the age of 12, upper limb dysfunction, respiratory failure, cardiomyopathy and a premature death. The median survival of boys and young men with DMD is 22–28 years, and only very few patients survive beyond the third decade. Approximately one third of individuals with DMD exhibit cognitive impairments due to the absence of brain-expressed dystrophin isoforms. These neurodevelopmental comorbidities contribute to motor function delays and can accelerate progression to wheelchair dependence and other DMD-related complications. DMD reduces a patient's strength, functional abilities, and overall QoL as the disease progresses, leading to a loss of autonomy and self-reliance.
Type of evidence for the clinical evaluation	Head-to-head study (EPIDYS) and MAIC (OLE study)
Most important efficacy endpoints (Difference/gain compared to comparator)	**EPYDIS study endpoints (i.e. 4SC, MRS of the VLFFL, NSAA)** as predictors of disease progression and disease milestones such as LoA, further investigated in OLE. **Age at loss of ambulation (long term OLE study + MAIC)**

Summary	
	Median age at loss of ambulation (LoA) for givinostat treated patients[1] was 17.97 years pre-weighting and not reached post-weighting, compared with 12.28 years for SoC treated patients (based on MAIC). The difference was statistically significant. Recent analysis from long term OLE trial (Study 51) show a LoA at 18.1 (*******) years for the patients treated with givinostat from study entry. **Age at non-invasive ventilation (OLE study + MAIC)** Median age at NIV for givinostat treated patients[1] was 27.0 years pre-weighting and not reached post-weighting, compared with 18.5 years for SoC treated patients (based on MAIC). The difference was statistically significant. **Age at forced vital capacity <1L (OLE study + MAIC)** Median age at FVC <1L for givinostat treated patients[1] was 34.9 years pre-weighting and not reached post-weighting, compared with 23.9 years for SoC treated patients (based on MAIC). The difference was statistically significant.
Most important serious adverse events for the intervention and comparator	Intervention: No serious TEAEs were considered related to the study drug or led to withdrawal. Comparator: No serious TEAEs were considered related to placebo or led to withdrawal
Impact on health-related quality of life	Clinical documentation: Measured using PODCI (EPIDYS) and PedsQL (OLE) (McAdam et al. 2025) Difference in PODCI LS means (givinostat-placebo): 2.96 (95% CI: -1.4111, 7.331) Health economic model: Better than comparator
Type of economic analysis that is submitted	Type of analysis: Cost-utility analysis Type of model: Markov model
Data sources used to model the clinical effects	MAIC based on givinostat clinical trials EPIDYS and Study 51 (OLE), as well as UK real-world data
Data sources used to model the health-related quality of life	In the cost-effectiveness model, health states utilities were derived from Audhya et al. (Audhya et al. 2023b)
Life years gained	****years
QALYs gained	**** QALY
Incremental costs	********** DKK
ICER (DKK/QALY)	******** DKK/QALY ********** DKK/QALY ********** DKK/QALY
Uncertainty associated with the ICER estimate	Most sensitive parameters: Givinostat compliance and discontinuation rates (compliance >98% in all groups), and patient utility values
Number of eligible patients in Denmark	Incidence: 5 Prevalence: 17
Budget impact (in year 5)	**********

[1] The analysis is based on givinostat treated cohort from the EPIDYS study and patients from Study 43 that met the EPIDYS inclusion criteria at treatment start continuing in the OLE study

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition

DMD is a severe, progressive, lethal, and life-limiting rare neuromuscular disorder characterized by ongoing, irreversible muscle degeneration. The disease leads to continuous muscle tissue loss, and importantly, the regenerative capacity of muscle is severely limited, resulting in cumulative degeneration and a fatal disease trajectory (Emery 2002, Hoffman et al. 1987). A disease overview for DMD is provided in Table 1. Additional information on DMD Aetiology, pathophysiology, diagnosis, course of the disease, complications, and burden of disease, is available in 0.

Table 1: Disease overview

Duchenne Muscular Dystrophy (DMD)
Aetiology and pathophysiology
• *DMD is a rare, rapidly progressing, and lethal neuromuscular disease. DMD is a genetic, X-linked recessive disorder, caused by mutations in the dystrophin gene, which primarily affects males (Ryder et al. 2017).*
• *Dystrophin is an important cytoskeletal protein part of the Dystrophin-Associated protein complex (DAPC) that supports the strength, stability, and functionality of muscle cells and is coded for by the dystrophin gene (Petrof et al. 1993, Le et al. 2018, Aartsma-Rus et al. 2016, Matsumura and Campbell 1994).*
• *Lack of dystrophin results in the disassembly of DAPC complexes leading to loss of muscle membrane integrity and disrupted muscle repair and regeneration processes (Bonilla et al. 1988, Dowling et al. 2023, Aartsma-Rus 2025). As part of the DMD pathology, histone deacetylase (HDAC) activity is constitutively increased, leading to epigenetic changes and inhibition of muscle regeneration factors, chronic inflammation, fibrosis, and adipogenesis (Minetti et al. 2006, Consalvi et al. 2013, Aartsma-Rus 2025).*
Epidemiology
• *DMD is a rare disease with an incidence of approximately 5 cases annually in Denmark and a prevalence of 150 (RehabiliteringsCenter for Muskelsvind 2024).*
Loss of motor function
• *DMD is characterised by concurrent, progressive injury of all muscles throughout the whole body starting at birth. Key milestones of disease progression are the LoA and the loss of upper limb function, including fine motor control followed by the loss of respiratory function and eventually loss of the ability to swallow (Walter and Reilich 2017).LoA represents a critical milestone in the progression of DMD. Following the loss of ambulation, the rate of disease progression accelerates significantly, with a rapid decline in functional abilities, including respiratory and cardiac function. This transition marks a period of increased deterioration and a higher rate of morbidity* and mortality (McDonald et al. 2024, Birnkrant et al. 2018b).

- *Delay in LoA and upper limb function are the key milestones of disease progression that have the most significant detrimental effect on health-related quality of life (HRQoL) in boys and young men with DMD and their caregivers (Walter and Reilich 2017, Andreozzi et al. 2022).*
- *Adolescence is usually a time of growing independence and autonomy, but boys and young men with DMD will need their parents to provide increasing help with activities of daily living (ADLs), including intimate and personal care, as their functional abilities continuously decline (Landfeldt et al. 2016b).*
- *Compared to boys and young men with DMD who still retain physical independence, wheelchair dependence, loss of upper limb function, and losing ability to swallow negatively impact HRQoL (Andreozzi et al. 2022). This emphasises the substantial impact of disease progression on patients' well-being.*
- *Loss of hand function prevents participation in most daily activities of adolescence, such as driving an electric wheelchair, eating, schoolwork, computer games and interacting with others on social media and is often considered more difficult than the transition to requiring a wheelchair (Eriksson et al. 2024, Bever et al. 2024).*

Complications

- *DMD patients experience life-threatening complications such as orthopaedic problems, respiratory complications, and cardiomyopathies which increase in severity as the disease progresses (Andrews and Wahl 2018, Schultz et al. 2022, Birnkrant et al. 2018c, Childs et al. 2024).*

Health related quality of life (HRQoL)

- *LoA is a key milestone in the depletion of HRQoL in DMD patients (Andreozzi et al. 2022).*
- *Lower levels of strength and slower rates of functional performance correlate with participation in fewer physical and social activities which have a significant negative impact on the HRQoL of DMD patients (Orso et al. 2023, Landfeldt et al. 2016a, Bendixen et al. 2014).*

Mortality

- *Respiratory and/or cardiac complications are the most common causes of death (Birnkrant et al. 2018c, Childs et al. 2024)*
- *DMD is associated with a premature death, the median survival of boys and young men with DMD is 22–28 year (Broomfield et al. 2023, Broomfield et al. 2021, Nart et al. 2024, Pietrusz et al. 2023). A Swedish report from the NMiS (Swedish National Registry for Neuromuscular Disorders) during 2025 for the company, estimated the median survival age at [redacted] years and the mean at [redacted] years (Italfarmaco 2025b) for DMD patients only treated with the standard of care (SoC). Rudolfsen et al. reported a mean age at death of 26.8 years (IQR: 19–34) in DMD patients in Denmark (Rudolfsen et al. 2024).*

Caregiver burden

- *Caregiver burden increases with disease progression, significantly impacting their overall quality of life (Donnelly et al. 2023, Porteous et al. 2021)*
- *Caregivers of boys and young men with DMD frequently experience anxiety, depression, and impaired mental health, as well as physical health issues due to the physically demanding nature of caring for a child/young adult with DMD (Donnelly et al. 2023, Porteous et al. 2021).*
- *Caregivers face constraints and costs that impact their health and financial well-being long beyond the usual period of childhood dependency (Schwartz et al. 2021).*
- *Grief is an inseparable aspect of parenting a child or young adult with DMD. Although at its most intense at the time of death of their child, parents experience grief before bereavement and at each disease progression point, such as loss of ambulation, requirement for enteral feeding, and need for non-invasive ventilation (Donnelly et al. 2023).*

DMD management requires a multidisciplinary approach

- *DMD is a complex, multisystem disease managed by a multidisciplinary team for which there is no cure. The goal of treatment is to allow boys and young men with DMD to experience as much of childhood as possible by slowing the progressive trajectory of muscle loss thereby maintaining independence and delaying the time to loss of ambulation and loss of upper limb function (RehabiliteringsCenter for Muskelsvind 2024)*
- *SoC for boys with DMD in Denmark includes physiotherapy, GCs and other supportive care (RehabiliteringsCenter for Muskelsvind 2024)*

There is a high unmet need for a new effective therapy for boys and young men with DMD that demonstrates a clinically meaningful and statistically significant improvement in functional endpoints compared with the current SoC regardless of specific dystrophin gene mutation type.

3.2 Patient population

Due to DMD being an X-linked recessive disorder, the condition almost exclusively affects boys (Emery 1991, Stark 2015). Data from Rehabilitationscenter for Muskelsvind, the most accurate source according to the DMC, shows the current prevalence to be approximately 150, and the incidence approximately 5 (RehabiliteringsCenter for Muskelsvind 2025). The prevalent DMD population has increased successively over the years, presumably due to improved survival as a result of the early use of respiratory care (Italfarmaco 2024c, Italfarmaco 2024e). However, this has not impacted on the important functional disease milestones such as LoA.

In a Danish study, the mean age at death was 26.8 years (IQR: 19 – 34) (Rudolfsen et al. 2024). The mean age of respiratory failure was 23.2 years of age, with 50% of patients at the age of 12–17 years been diagnosed with respiratory failure (Rudolfsen et al. 2024).

Similar to other Nordic countries, Danish DMD patients are treated with a daily GC regimen in accordance with international guidelines. A Norwegian study examining the genetic and clinical characteristics of pediatric DMD reported an average age at diagnosis of 3.9 years (SD ± 2.0) (Annexstad et al. 2019). In this cohort, GC treatment, recognized as the standard of care, was initiated in 78% of patients at a mean age of 5.8 years (SD ± 1.5). Over a 3.5-year follow-up period, 23 boys (35%) experienced LoA, with the average age at LoA being 11.1 years (SD ± 2.1) among those treated with GCs. Danish experts confirmed that these findings are consistent with data from Denmark (Italfarmaco 2024c).

The eligible population are boys with a confirmed DMD diagnosis aged ≥6 years who are ambulant at initiation of givinostat treatment and treatment duration should be guided by clinical judgment and continued for as long as there is evidence of patient benefit.

It is expected that the initial patient population in consideration for givinostat treatment (prevalent population) during the first couple of years after drug recommendation will include boys aged 6 years and above, in an early or late ambulatory phase of the disease following the inclusion criteria of the EPIDYS study (4SC & TTR). However, once the drug is established and a steady state is reached after the initial “catch-up phase” initiation, treatment would be in the youngest patients only, i.e. the incident population (approximately 5 patients per year). In this steady-state population, the typical patient is approximately 6 years of age and in an early ambulatory state of the disease at treatment initiation (Italfarmaco 2024c). Hence, we refer to givinostat treatment for the incident population as the Danish “clinical practice steady state”, which should represent the decision problem for the major part of the drug’s availability on the market (Table 2).

Incidence and prevalence in Denmark are based on data from RehabiliteringsCenter for Muskelsvind (see Table 2) (RehabiliteringsCenter for Muskelsvind 2024). A systematic review of 44 studies showed that the pooled global DMD prevalence was 2.8 cases per

100,000 in the general population, while the pooled global DMD birth prevalence was 19.8 per 100,000 live male births (Crisafulli et al. 2020). Global prevalence per year was roughly estimated assuming 2.8 cases per 100,000 multiplied with the global number of males per year.

Table 2: Incidence and prevalence in the past 5 years

Year	2019	2020	2021	2022	2023
Incidence in Denmark*	5	5	5	5	5
Prevalence in Denmark*	150	150	150	150	150
Global prevalence	110 000	111 000	112 000	113 000	114000

*= Number informed by Rehabiliteringscenter for Muskelsvind via email 3 Feb 2025. It was not possible to get numbers for 2019-2021 for prevalence, but numbers are most likely a bit lower than 150.

The estimated number of patients eligible and expected to be treated with givinostat over the next 5 years is presented in Table 3. Numbers are calculated based on the incident number of patients, and the share of prevalent patients who are still early ambulatory. Prevalent patients will start-up givinostat treatment during the first year and by the end of the second year all eligible prevalent patients are estimated to have started treatment. From year 3 and onwards, only incident patients at age 6 will be initiated on treatment.

Table 3: Estimated number of patients eligible for treatment

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for treatment in the coming years	9	13	3	3	3

3.3 Current treatment options

DMD is a complex, multisystem disease managed by a multidisciplinary team. The only available treatment in the EU for DMD is glucocorticoids (GCs), which are recognized as the standard pharmacological management.

Research is ongoing for dystrophin replacement therapies, including antisense oligonucleotide-based treatments and gene therapies, these dystrophin-restoring treatments restore only partially functional dystrophins that may slow down disease pathology, but the pathophysiological processes remain inevitable (Pascual-Morena et al. 2020). Furthermore, developing therapies that can address the many downstream consequences of the absence of dystrophin such as muscle fibre injury, chronic inflammation, impairment of muscle regeneration mechanisms and fibrogenesis and adipogenesis, are needed to improve patient functions and QoL. Such therapies would have a different mechanism of action (MoA), activating alternative receptors and signalling pathways than GCs (Birnkrant et al. 2018a).

3.3.1 DMD treatment guidelines

In Denmark, like other European countries such as UK or the rest of Nordic countries, the management of DMD adheres to the international guidelines (Birnkrant et al. 2018a, Birnkrant et al. 2018d, Birnkrant et al. 2018c), that provides a multidisciplinary approach to DMD care, emphasizing the importance of coordinated management across various specialties. The goal of treatment is to allow boys and young men with DMD to experience as much of childhood as possible by slowing the progressive trajectory of muscle loss thereby maintaining independence and delaying the time to LoA and loss of upper limb function (Figure 67) (Birnkrant et al. 2018a, Birnkrant et al. 2018d, Birnkrant et al. 2018c).

3.3.1.1 Clinical practice in Denmark

In Denmark, the treatment of boys and young men with DMD is carried out at a highly specialised level. Regular check-ups by specialists and therapists are carried out with the aim to initiate treatment for prevention of complications at the optimal time point.

Currently, all boys are offered standard treatment, as it can delay the progression of the disease and reduce muscle loss. Prednisolone and deflazacort are the two types of GCs used in the treatment of DMD. However, some boys have to terminate treatment due to side effects (Section 3.3.2.1) (RehabiliteringsCenter for Muskelsvind 2024). As the high doses of GC treatment increase the risk of osteoporosis, preventive osteoporosis treatment is standard. DEXA scans are performed every 2-3 years to monitor the development (RehabiliteringsCenter for Muskelsvind 2024).

Lung function and vital capacity is measured regularly in connection with neurological check-ups. If lung function is significantly affected, or there are problems with repeated lung infections and mucus problems, a referral is made for further examination at a respiratory center (Italfarmaco 2024c). A cough machine or a CPAP machine is offered to handle respiratory problems. Eventually, breathing problems during sleep will become so severe that it is necessary to support breathing with either NIV treatment or an invasive respirator (RehabiliteringsCenter for Muskelsvind 2024). In their study, Rudolfsen et al. reported respiratory failure in 73% of Danish individuals with DMD, with the prevalence increasing to 86% among those aged 8 years and older. Mean age at first respiratory mask treatment was 15.3 years (SD: 6.7 years). Start of in-home mechanical respirator was at mean age 23.2 (Rudolfsen et al. 2024).

To prevent or delay the progression of cardiomyopathy in DMD, treatment with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), and in selected cases β-blockers, is recommended. Clinical guidelines advise initiation of such therapy early in the disease course, ideally before the age of 10 years (Birnkrant et al. 2018c). As the cardiomyopathy progresses, arrhythmias may occur, and some may need to be treated with a pacemaker (RehabiliteringsCenter for Muskelsvind 2024). In Danish individuals with DMD 12 years of age or older, 59% were diagnosed with heart disease (Rudolfsen et al. 2024).

In Denmark, rehabilitation is a central component of DMD management, including early physiotherapy to preserve flexibility and delay joint contractures. Night splints, casting, or surgery may address Achilles tendon tightness. Assistive devices and personal support are routinely required. Adapted, low-intensity exercise is recommended to maintain function, while excessive exertion is avoided to prevent muscle damage (RehabiliteringsCenter for Muskelsvind 2024). In the study by Rudolfsen et al. (2024), 35% of individuals with DMD underwent Achilles tendon surgery before the age of 18 (Rudolfsen et al. 2024).

In the same study, scoliosis was reported in 57% of patients, and scoliosis surgery was needed in 31% of those patients. The condition is more likely to develop in individuals who lose ambulation early, often before reaching full growth. Use of rigid corsets following LoA may help support posture and delay progression, however scoliosis surgery is necessary to correct and stabilize spinal alignment, improving comfort and sitting balance in more severe cases (Rudolfsen et al. 2024). Treatment with GCs has had a major effect on the development of scoliosis; whereas back surgery was previously necessary for almost all young boys with DMD, today only a small proportion of boys undergo surgery (RehabiliteringsCenter for Muskelsvind 2024).

3.3.2 Pharmacological treatment of DMD

3.3.2.1 Glucocorticoids (GCs)

To date, no therapy has demonstrated a statistically and clinically meaningful benefit over the existing SoC, and GCs continue to represent the only available approved therapeutic option in the EU.

GCs act as anti-inflammatory and immunosuppressive agents, effectively controlling symptoms, maintaining muscle strength, and delaying the LoA. In a Norwegian study, boys treated with GCs lost ambulation 1.7 years later than those who were not, though with significant variability (Annexstad et al. 2019). However, the benefit of GCs in slowing disease progression is limited, as demonstrated in a Cochrane meta-analysis, which found evidence supporting short-term (6 months to 2 years) improvements in muscle strength and function but no clear prolongation of independent walking (Manzur et al. 2008).

The choice of GC (Prednisone/prednisolone and deflazacort) remains a subject for consideration and may depend on individual patient factors (Matthews et al. 2016). In Denmark, DMD patients are on daily GC regimens, majority first on prednisolone and many then switching to deflazacort (Italfarmaco 2024c).

Recently, the dissociative GC vamorolone was approved for the treatment of DMD (European Medicines Agency 2024b). In Denmark, vamorolone is yet to be available for patients, but request for assessment has been submitted (Medicinrådet 2025b).

3.3.2.2 Ataluren (Translarna)

Ataluren was granted a conditional marketing authorisation in the European Union in July 2014 for the treatment of DMD resulting from a nonsense mutation in the dystrophin gene in ambulatory patients aged two years and older. The primary endpoint for the pivotal Phase 3 trial was not met (McDonald et al. 2017) and the marketing authorisation was withdrawn by EMA in 2025. (European Medicines Agency 2024a). It was never approved for reimbursement in Denmark.

3.4 The intervention

Givinostat is the first HDAC inhibitor indicated for the treatment of DMD patients regardless of genetic mutation, that has been evaluated in a robust clinical program in DMD with more than 200 patients recruited.

In DMD, the absence of functional dystrophin leads to the disassembly of DAPC complexes directly weakening the muscle cell membrane, leading to muscle cell damage contributing to disease progression (Bonilla et al. 1988, Mozzetta et al. 2024). Indirectly, it triggers a cascade of pathological events within muscle cells, including chronic inflammation and impaired muscle repair and regeneration processes (Dowling et al. 2023).

DAPC disassembling leads to HDAC hyperactivation, a core element of the DMD pathophysiology, resulting in epigenetic changes causing inhibition of muscle regeneration factors, chronic inflammation, and replacement of muscle tissue with fibrotic and fat tissue (Figure 64 in Appendix L) (Bez Batti Angulski et al. 2023, Consalvi et al. 2011, Giuliani et al. 2022, Sandonà et al. 2023b, Colussi et al. 2008, Consalvi et al. 2013).

Targeting HDAC activity through pharmacological inhibition has been shown to counteract these pathological mechanisms by restoring muscle homeostasis, reducing fibrosis and inflammation, and slowing disease progression in preclinical and clinical DMD studies (Bettica et al. 2016, Mozzetta et al. 2024, Mercuri et al. 2024b, Lamb 2024). Given that DMD involves irreversible muscle degeneration, early therapeutic intervention is crucial to maximizing functional preservation and delaying key disease milestones (Birnkrant et al. 2018a, Aartsma-Rus et al. 2019).

An overview of givinostat is provided in Table 4.

Table 4: Overview of the intervention

Overview of intervention	
Indication relevant for the assessment	Ambulant DMD patients aged 6 years and above on stable GC treatment
ATMP	Not applicable
Mode of Action	Givinostat is a novel class I and II histone deacetylase HDACi, orally administered, designed to target HDAC hyperactivation in DMD, that by modulating aberrant gene expression and cell signalling in the muscle, restores muscle homeostasis and promotes muscle regeneration, reduces inflammation, fibre cell injury, intramuscular fibrosis and fatty replacement while promoting myogenesis in patients with DMD (Cazzaniga et al.

Overview of intervention	
	2018, Licandro et al. 2021). As a result, givinostat mitigates the pathological downstream effects originated by the absence of dystrophin without correcting the primary genetic defect (Licandro et al. 2021, Sandonà et al. 2023a). Givinostat is the first nonsteroidal treatment for DMD approved for use irrespective of the underlying dystrophin gene mutation causing the disease. More information regarding givinostat mechanism of action is found in Appendix 0.
Method of administration	Oral suspension
Dosing	According to SmPC: Twice daily orally, following a weight-based scheme (22.2mg/2.5 mL at lowest weight ≥15 kg, and 53.2 mg/6.0 mL at highest weight ≥60 kg (European Medicines Agency 2025); see Section 3.4.1.1.
Dosing in the health economic model (including relative dose intensity)	According to SmPC: Twice daily orally, following a weight-based scheme (22.2mg/2.5 mL at lowest weight ≥15 kg, and 53.2 mg/6.0 mL at highest weight ≥60 kg (European Medicines Agency 2025)
Should the medicine be administered with other medicines?	Givinostat should be used in combination with GCs
Treatment duration / criteria for end of treatment	The decision to continue treatment in patients who become non-ambulatory should be taken at the discretion of the treating physician based on the overall benefit and risk assessment. The health economic analysis assumes that treatment is discontinued when patient starts full-time ventilation.
Necessary monitoring, both during administration and during the treatment period	Baseline platelet counts and triglycerides should be obtained and evaluated prior to initiation of treatment and monitored during treatment to determine if dosage modifications are needed. In addition, in patients with underlying cardiac disease or taking concomitant medications that cause QT prolongation, an ECG should be obtained when initiating treatment, during concomitant use, and as clinically indicated.
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	No other test is needed than what is used in clinical practice for a diagnosis of DMD.
Package size(s)	Bottle with 140 mL of givinostat 8.86 mg/mL oral suspension (European Medicines Agency 2025)

3.4.1.1 Posology

The expected dosing of givinostat is in accordance with the recommended dosage presented in the SmPC (Table 5). In case of adverse reactions, the dosage will be modified according to recommendations in the SmPC (Table 6).

Table 5: Recommended dosage of givinostat

Weight	Dosage	Oral suspension volume
15 kg to less than 20 kg	22.2 mg twice daily	2.5 mL twice daily
20 kg to less than 40 kg	31 mg twice daily	3.5 mL twice daily
40 kg to less than 60 kg	44.3 mg twice daily	5 mL twice daily
60 kg or more	53.2 mg twice daily	6 mL twice daily

Reference: Givinostat SmPC (European Medicines Agency 2025)

Table 6: Dosage modifications for adverse reactions

	First dosage modification		Second dosage modification	
Weight	**Dosage**	**Oral suspension volume**	**Dosage**	**Oral suspension volume**
15 kg to less than 20 kg	17.7 mg twice daily	2 mL twice daily	13.3 mg twice daily	1.5 mL twice daily
20 kg to less than 40 kg	22.2 mg twice daily	2.5 mL twice daily	17.7 mg twice daily	2 mL twice daily
40 kg to less than 60 kg	31 mg twice daily	3.5 mL twice daily	26.6 mg twice daily	3 mL twice daily
60 kg or more	39.9 mg twice daily	4.5 mL twice daily	35.4 mg twice daily	4 mL twice daily

Reference: Givinostat SmPC (European Medicines Agency 2025)

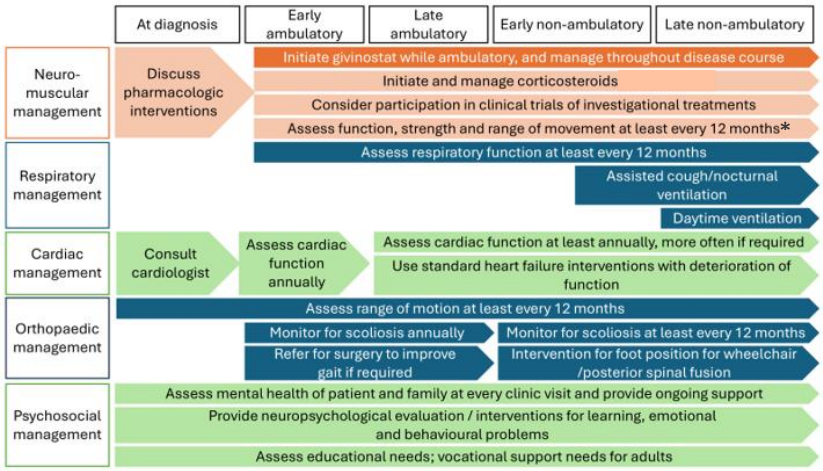
3.4.2 Description of ATMP

Not applicable

3.4.3 The intervention in relation to Danish clinical practice

The proposed place in the current treatment algorithm for givinostat with concomitant SoC (GC) is as first line treatment initiated while patients are ambulatory (Figure 1). Givinostat is hence not intended to displace GC use in clinical practice.

Figure 1: Proposed place in therapy for givinostat



Notes: * In Denmark this is every 6 months (Italfarmaco 2024c, Italfarmaco 2024e)
References: Adapted from Birnkrant et al. (2018a), Birnkrant et al. (2018c), and DMD Care UK (2024)

3.5 Choice of comparator(s)

Givinostat is approved with concomitant SoC, which consists of GCs and a number of non-pharmacological interventions (described in detail in section 3.3). Thus, the relevant pharmacological comparator to givinostat plus GCs is GCs alone (placebo added in the clinical trial). The GCs typically recommended in the treatment of DMD and in Danish

clinical practice are prednisolone (starting dose 0.75 mg/kg/day) and deflazacort (starting dose 0.6 mg/kg/day) (RehabiliteringsCenter for Muskelsvind 2025). According to a Danish clinical expert, the dosage of deflazacort in clinical reality is 0.9 mg/kg/day (Italfarmaco 2024c). In the CEM it was assumed that 20.47% receive prednisolone and 79.53% receive deflazacort, corresponding to adjusted EPIDYS data (ClinicalTrials.gov 2023a). These specific GCs and their shares correspond well with the GC treatment used in clinical practice in the Nordics, as a Danish clinical expert informs that most patients start on treatment with prednisolone but switch to deflazacort at the occurrence of adverse events (Italfarmaco 2024c).

Table 7: Overview of comparator (no treatment in addition to prednisolone or deflazacort)

Overview of comparator	
Prednisolone 20.47 % of patients	
Generic name	Prednisolone
ATC code	H02AB07
Mechanism of action	Targets the GC receptor to suppress pro-inflammatory signalling pathways. Mechanism of action in DMD specifically is not fully understood.
Method of administration	Oral
Dosing	0.75 mg/kg/day (RehabiliteringsCenter for Muskelsvind 2025)
Dosing in the health economic model (including relative dose intensity)	0.75 mg/kg/day (RehabiliteringsCenter for Muskelsvind 2025)
Should the medicine be administered with other medicines?	No
Treatment duration/ criteria for end of treatment	Continuous treatment without end criteria (until patients can no longer swallow)
Need for diagnostics or other tests (i.e. companion diagnostics)	No
Package size(s)	100 tablets * 5 mg
Deflazacort (79.53% of patients)	
Generic name	Deflazacort
ATC code	H02AB13
Mechanism of action	Targets the GC receptor to suppress pro-inflammatory signalling pathways. Mechanism of action in DMD specifically is not fully understood.
Method of administration	Oral
Dosing	0.6 mg/kg/day (RehabiliteringsCenter for Muskelsvind 2025)
Dosing in the health economic model (including relative dose intensity)	0.9 mg/kg/day (Italfarmaco 2024c)
Should the medicine be administered with other medicines?	No
Treatment duration/ criteria for end of treatment	Continuous treatment without end criteria (until patients can no longer swallow)
Need for diagnostics or other tests (i.e. companion diagnostics)	No
Package size(s)	60 tablets * 6 mg

Abbreviations: GC: Glucocorticoid

3.6 Cost-effectiveness of the comparator(s)

No GCs have been evaluated by the DMC for the treatment of DMD. However, they have a relatively low cost and can be assumed to be cost-effective.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

As no single test exists that evaluates disease evolution in all muscle groups, regulatory bodies recommend that applicants evaluate treatment effects using multiple tests in support of the selected primary outcome measure (European Medicines Agency 2016, Center for Drug Evaluation and Research 2020). Study endpoints consisted of timed functional test, muscle strength, imaging test (MRS), age to achieve disease milestones and safety. Study endpoints and their definitions are shown in Table 8.

Table 8: Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Change from baseline in the standard 4SC assessment [EPIDYS; primary endpoint]	18 months	Mean change in time to climb 4 standard stairs before and after 18 months of treatment of givinostat vs. placebo.	In addition to the 4SC recorded in seconds, functional adaptation employed by the boy during the test was evaluated and graded by functional evaluators according to standardised scales (Table 58, Appendix 0).
Change from baseline in NSAA total score [EPIDYS; key secondary endpoint]	18 months	Change from baseline in the total NSAA score to after 18 months of treatment with givinostat or placebo.	The total NSAA score was calculated as the sum of the scores for each of the items (Table 58, Appendix 0).
NSAA cumulative loss of function [EPIDYS; key secondary endpoint]	18 months	The boy's cumulative number of failures across all post-baseline visits was the endpoint of interest for analysis (sum of the total failures at each post-baseline visit).	For each boy at each post-baseline visit performance of each of the 17 items of the NSAA was assessed (Table 58, Appendix 0).
Change from basline in Time-to-rise from floor (TTRF) [EPIDYS; key secondary endpoint]	18 months	Mean change from baseline in time to rise from the floor after 18 months of treatment with givinostat vs. placebo.	Time to rise from the floor was graded by functional evaluators according to standardised scales (Table 58, Appendix 0)
Change from baseline in 6 minute walk test (6MWT)	18 months	Mean change from baseline in 6MWT after 18 months of treatment with givinostat vs. placebo.	Boys who stopped the test prematurely were still included in the summaries, plots and analyses of the total distance walked by the end of

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
[EPIDYS; key secondary endpoint]			the test and the number of falls (Table 58, Appendix 0).
Change from baseline in muscle strength [EPIDYS; key secondary endpoint]	18 months	Mean change from baseline to 18 months after treatment with givinostat vs. placebo in muscle strength was evaluated by knee extension and elbow flexion.	Muscle strength was evaluated by knee extension and elbow flextionand measured by HHM (Table 58, Appendix 0).
Change from baseline in VL MFF [EPIDYS; key secondary endpoint]	18 months	Mean change in VL MFF was assessed by MRS before and after 18 months of treatment with givinostat vs. placebo.	Analysis of this endpoint only applied to the MR cohort, i.e. those who completed MR assessment at baseline, 12 and 18 months (Table 58, Appendix 0).
Change from baseline in quality of life, PODCI [EPIDYS; exploratory endpoint]	18 months	A total of 5 subscales (upper extremity function; transfer and basic mobility; sports and physical functioning; pain/comfort and happiness) and 1 global function scale were calculated from the questionnaire.	The endpoints of interest were the change from baseline to 18 months in the standardised scores for each subscale and the global function scale, as completed by the parent and the boy (Table 58, Appendix 0).
Health related quality of life [OLE; exploratory endpoint]	Week 48 and then yearly till end of study	Change in patient and/or parent/caregiver reports of quality of life as measured by PedsQL	The Paediatric Quality of Life Inventory (PedsQL) Core and Neuromuscular modules were performed at baseline (Visit 1), yearly and at the end of study (Table 58, Appendix 0).
Age at LoA [EPIDYS/OLE (exploratory endpoints) and the UK Real World Data study; used in the MAIC]	Baseline through end of study #	In EPIDYS/OLE, loss of ambulation is defined as satisfying both the following criteria at the same visit: • Subject is unable to perform the 6MWT due to physical inability. • Subject is unable to complete the 10-metre walk/run test in 30 seconds or less without any support or devices (10-metre walk/run test grading ≤2). In the UK Real World Data study, loss of ambulation was defined as “not able to walk 10 meters without assistance”	• A subject is considered as unable to perform the 6MWT due to physical inability if missing 6MWT values were imputed as Class 2 missing values, as per study definition. • A subject is unable to complete the 10-metre walk/run test in 30 seconds or less if fastest time to walk 10 meters is > 30 or 10 meter walk qualitative grade ≤ 2. Time to loss of ambulation is calculated in days considering: Date ambulation lost – date of first administration of study treatment + 1. In the UK Real World Data study, data was collected with 6 month intervals, using the North Star Physiotherapy Assessment (v1.2, January 2023)

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Age at NIV [EPIDYS/OLE (exploratory endpoints) and the UK Real World Data study; used in the MAIC]	Baseline through end of study #	NIV refers to the provision of ventilatory support through the patient's upper airway using a mask or similar device without intubation. In OLE, NIV was defined as age at respiratory support needed during the day. Exact definition of NIV not reported in the UK Real World Data study.	As there were only 2 events for age at respiratory support in Study 51, comparative data was generated from age at LoA data using the multiplying factor estimated from the NS data, thereby ensuring alignment with the NIV definition in the UK Real World Data study In the UK Real World Data study, data was collected with 6 month intervals, using the North Star Physiotherapy Assessment (v1.2, January 2023)
Age at FVC < 1L [EPIDYS/OLE (exploratory endpoints) and the UK Real World Data study; used in the MAIC]	Baseline through end of study #	Forced vital capacity (FVC) is defined as the total volume of air that can be forcibly exhaled after a full inspiration. It is measured in liters and used to assess respiratory function, particularly in restrictive and obstructive pulmonary disorders. Absolute FVC refers to the raw, unadjusted measurement of lung volume exhaled, expressed in litres (L). FVC <1L is defined as having a forced Vital Capacity less than one liter. FVC <1L was not a predefined endpoint in EPIDYS/OLE, but can be calculated as FVC was measured.	In EPIDYS/OLE, FVC was collected as per the site's standard process at the visits. At each assessment, three studies with maximal effort was attempted by each subject. In the UK Real World Data study, data was collected with 6 month intervals, using the North Star Physiotherapy Assessment (v1.2, January 2023)

* Time point for data collection used in analysis (follow up time for time-to-event measures)

Note: the outcomes were collected at the December 2023 data-cut for pooled givinostat data set, mean actual duration of givinostat treatment was 1,177 days (SD: 453 days). The UK Real World Data study was a retrospective case note study, with age at last assessment 21.19 years (SD: 2.76) and 21.29 years (SD: 3.95) in the GC continued and GC stopped group respectively)

References: EPIDYS Lancet Neurol publication (Mercuri et al. 2024b, Mercuri et al. 2024c); EPIDYS CSR (2022) (Italfarmaco 2022a); EPIDYS SAP (2022) (Italfarmaco 2022b).

3.7.1.1 Validity of outcomes

The validity of study endpoints such as the 4SC, NSAA and other timed function tests has been widely recognized in clinical trials. Clinical trials for DMD often begin at a young age due to the progressive nature of the disease and the importance of early intervention in slowing disease progression. Functional tests, such as the 4SC, and NSAA are commonly

used as key endpoints in these trials. These tests are valid predictors of disease milestones such as the LoA, and disease progressions (McDonald et al. 2010a, Bushby et al. 2010). Similar measurements of vastus lateralis fat fraction using MRS have been shown to correlate with functional decline and serve as a predictor for the LoA in DMD patients (Barnard et al. 2020). LoA, in its turn acts as a predictor for respiratory decline. Furthermore, forced vital capacity (FVC) is recognized as a crucial predictor for survival, reflecting the progressive respiratory impairment associated with DMD. A value of < 1 liter typically indicates severe respiratory muscle weakness. This threshold is often used as a clinical marker of advanced pulmonary decline in neuromuscular diseases like DMD.

Validity of outcomes is thoroughly described in Appendix 0.

4. Health economic analysis

The developed health economic model aims to evaluate the cost-effectiveness of givinostat with concomitant GCs for the treatment of ambulant DMD patients aged 6 years or older, compared with the current management without givinostat, henceforth SoC for DMD. Total costs and DMD-related health outcomes, including QALYs, over a lifetime perspective are calculated for each treatment strategy, and the incremental differences between treatment arms for each measure are also calculated. Cost-utility results are expressed in terms of the incremental cost (DKK) per QALY gained.

4.1 Model structure

A Markov model previously developed as a part of the Project HERCULES (PH) was leveraged for the development of the CEM of givinostat in DMD. PH is a multinational collaboration set up by Duchenne UK together with patient organisations, HTA agencies, companies and other advisors to build a better evidence base to support HTA and reimbursement decisions for new treatments for DMD (Duchenne UK 2025b).

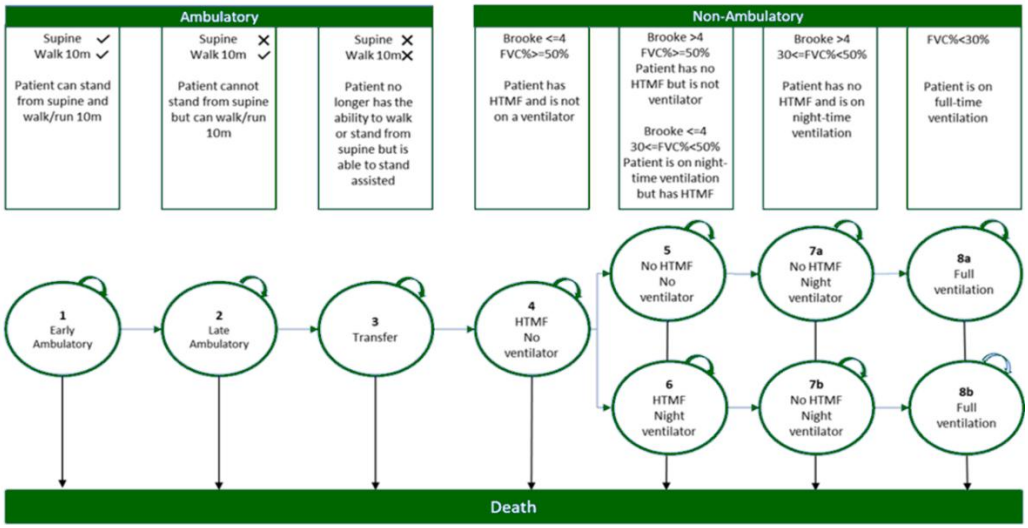
An SLR identified that there was a paucity of natural history data in DMD capturing the full patient pathway. This limited the ability of CEMs to fully capture the potential benefit of new treatments. Therefore, PH developed a new natural history model (NHM) (Broomfield et al. 2024) to support future economic evaluation for new DMD treatments. PH also had the aim of identifying and defining health states, mapping available data to these states, determining transition intensities between states under the current SoC, evaluating the impact of patient characteristics on these intensities, predicting the proportion of patients in each state at different times, and quantifying the mean time spent in each state (Broomfield et al. 2024). The health states modelled in PH underwent a validation process where they were presented to stakeholders which were both neuromuscular specialists, caregivers and representatives from PH. The final health states were shared with clinical experts for validation. The process of validation was to ascertain that the model structure reflected clinical experience, disease progression and health-related quality of life (Broomfield et al. 2024).

The structure of the NHM developed by PH comprises of ambulatory and non-ambulatory health states, plus an intermediate ‘transfer’ health state, and death as

depicted in Figure 2. The transfer health state is included in the base case as it is deemed crucial by caregivers and patients and marks an important stage in the disease progression. It is a key addition to this model compared with NHMs previously described in literature (Mercuri et al. 2024b)**.** See Appendix M for further description.

The model includes distinct health states that capture the disease's progression within each phase. These phases include the deterioration of ambulatory functions, the inability to stand and bear weight, and the progressive decline of upper body and respiratory functions in non-ambulatory patients. The health states defined within the model are reflective of the natural history of DMD, as identified by clinicians, patients, and caregivers, and are delineated using clinical practice measures. Patients may die at any time point in the model. Death is an absorbing state. Costs are assigned to each health state, and utilities are applied according to patients' disease progression status.

Figure 2: Schematic Diagram of the Model Structure



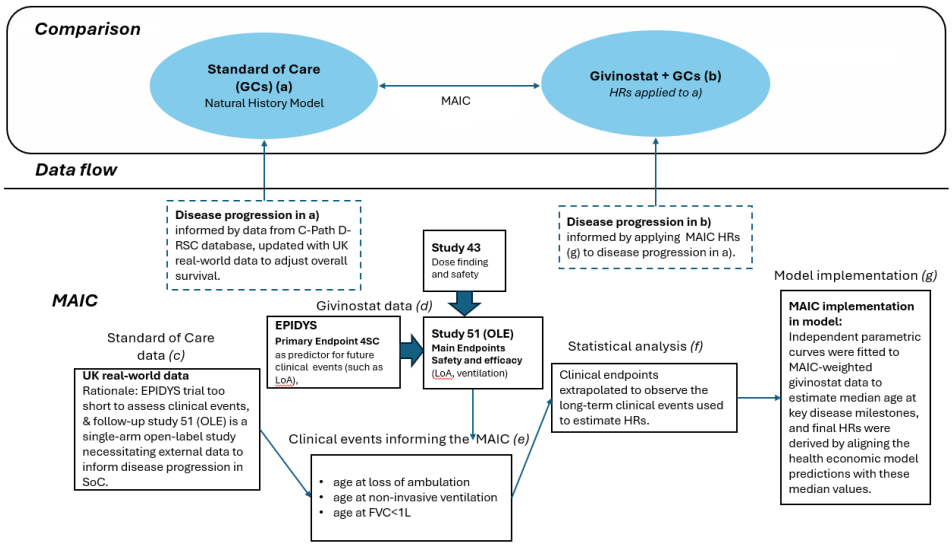
Abbreviations: HTMF: Hand-to-Mouth Function; FVC: Forced Vital Capacity

Patients can transition from health state (3) to the non-ambulatory health states as depicted in Figure 2. Patients transitioning from the health state (4) are split into one of two pathways depending on which function (HTMF or independent breathing) is lost first. Patients cannot transition between (5) and (6). In health states (7a) and (7b), patients have lost HTMF and require night-time ventilation. In health states (8a) and (8b), patients require full-time ventilation. The distinction between health states (8a) and (8b) is the route by which the patient cohort reached these states. Whilst transition probabilities in the CEM vary according to each pathway, the utilities and costs accrued in health states (7a) and (8a) are aligned with (7b) and (8b), respectively.

The patient pathway through the stages were confirmed by a Danish expert in neuromuscular disease (in Denmark the mean LoA is 10-12 years and similar to Norway, where mean LoA is 11.1 ± 2.1 years for patients on GC treatment and Sweden where mean LoA is [redacted] years and median LoA is 11 years) (Italfarmaco 2025b, Italfarmaco 2024c, Annexstad et al. 2019).

To predict disease progression in patients treated with givinostat, the model applies treatment effects in terms of HRs to the NHM (described above). Figure 3 gives an overview of how indirect treatment effect data were included in the model. First, the comparison between SoC and givinostat is depicted. Data used to inform disease progression for patients treated with GCs are sourced from the C-Path D-RSC database and updated with UK real-world data to adjust overall survival (see section 8.1.1.1) (box a). The treatment effects for givinostat are informed by MAICs. Since capturing long-term clinical outcomes within a single RCT placebo-controlled trial, like the EPIDYS study, is unfeasible and given that the follow-up Study 51 (OLE) was a single-arm, open-label trial, external real-world UK data on SoC were utilized in the MAIC analyses (see section 8.1) (see box c). However, data on clinical endpoints (box e) were immature, with no observed events within the trial period. Consequently, extrapolation was required to estimate long-term clinical outcomes and derive HRs (see section 8.1.1) (box f). Lastly, the HRs from the MAICs were recalculated for inclusion in the model (box g), as clinical events depend on transitions between multiple health states rather than a single state. For example, LoA is influenced by multiple transitions and cannot be directly assigned a single MAIC HR. Therefore, independent parametric curves were fitted to the MAIC-weighted givinostat data to estimate median ages for key disease milestones: LoA, need for NIV, and forced vital capacity (FVC) <1L (see section 8.1.1.2). The final HRs for the health economic model were derived by calibrating the model to predict the same median ages for these milestones as those extrapolated from the MAIC weighted data.

Figure 3: Overview indirect treatment effect data in health economic model



Abbreviations: 1L: 1 litre; FVC: Forced vital capacity; GCs: Glucocorticoids; HR: Hazard ratio; MAIC: Matching-adjusted indirect comparison; OLE: Open-label extension of the EPIDYS study; SoC: Standard of care

4.1.1 Model features

The features of the health economic model are presented in Table 9.

Table 9: Features of the economic model

Model features	Description	Justification
Patient population	Early ambulant DMD boys (≥6 years) on stable on GC treatment (incident population)	In line with patient population to be treated in Danish clinical practice when looking into the long-term perspective
Perspective	Extended health-service perspective	Patient time and transportation costs excluded due to lack of data
Time horizon	Lifetime (50 years)	To capture all health benefits and costs in line with DMC guidelines
Cycle length	One month	Considered adequate as it captures all relevant patients' benefits and costs within the health states and ensures that patients do not transition to more than one health state within one cycle of the model.
Half-cycle correction	Yes	
Discount rate	3.5%	The DMC applies a discount rate of 3.5 % for all years
Intervention	Givinostat + GCs	
Comparator(s)	Standard of care (SoC) consisting of GCs	The only available treatment in EU. GCs are recognized as the standard pharmacological management of DMD in Denmark
Treatment length	Patients treated with givinostat and GCs are assumed to discontinue treatment at full-time ventilation.	Treatment duration in clinical practice is uncertain, and no patients reached late stage disease in the trial and they are hence still on treatment. The decision to continue treatment in patients who become non ambulatory should be taken at the discrtion of the physician based on the overall risk/benefit assessment
Outcomes	Median age at: Unable to stand from supine; LoA; Loss of HTMF; Starting ventilation and Death	Outcomes that are important in clinical practice to measure disease progression.

Abbreviations: DMD: Duchenne muscular dystrophy; GC: Glucocorticoid; HTMF: Hand-to-mouth function

5. Overview of literature

5.1 Literature used for the clinical assessment

A comprehensive SLR was conducted to identify all published evidence of the clinical efficacy, safety and tolerability of givinostat and established clinical management (ECM) for DMD. The searches were originally performed on 08 May 2024 for databases and 09–13 May 2024 for congresses and health technology assessment (HTA) bodies. The latest update was performed in November 2024, with database searches on the 07–08 November, and hand searches on 06 November. The literature search is presented in detail in Appendix H. The studies included in the MAIC (section 7) are summarised in Table 10. In addition, Broomfield et al. (2024) is in the cost-effectiveness model used as the basis for natural history transition probabilities. Moreover, Pietrusz et al. (2023) and McDonald et al. (2018) are used as basis for share of patients on GCs without givinostat that receive spinal fusion surgery and time to surgery after loss of ambulation respectively. Also the range in age to be eligible for spinal fusion surgery is sourced from McDonald et al. (2018) (Table 10).

Table 10: Relevant literature included in the assessment of efficacy and safety [sample text in table for full paper, data on file and conference abstract]

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Mercuri et al. (2024b). Safety and efficacy of givinostat in boys with Duchenne muscular dystrophy (EPIDYS): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet. Neurology, 23(4), 393–403	EPIDYS	NCT02851797	Study start: 2017-06-06 Study completion: 2022-02-22	Givinostat + GCs vs. placebo + GCs for ambulant male patients aged at least 6 years with genetically confirmed duchenne muscular dystrophy
Study 51 Clinical Study Report. 5th interim analysis 31 Dec 2023. Version 1.0, 25 June. Italfarmaco. Data on file 2024 (Italfarmaco 2024s)	OLE (Study 51)	NCT03373968	Study Start: 2017-10-24 Study completion: at market authorization Latest cut-off: 2023-12-31	Givinostat + GCs (single arm) for patients who have participated in one of the previous studies with givinostat in DMD
Pietrusz et al. (2023). The effect of corticosteroid treatment on pulmonary function in adults with Duchenne muscular dystrophy. Poster Pietrusz (2024). Natural history of DMD cohort attending Neuromuscular Service National Hospital for Neurology and Neurosurgery, Queen Square, London. PowerPoint presentation. Not published	UK real-world data study	NA	Data was collected between February 2020 and July 2022	GCs in adults with DMD

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Broomfield et al. (2024). Developing a Natural History Model for Duchenne Muscular Dystrophy. Pharmacoecon Open, 8, 79-89.	NA (part of project HERCULES)	NA	NR	NA
McDonald et al. (2018). Long-term effects of glucocorticoids on function, quality of life, and survival in patients with Duchenne muscular dystrophy: a prospective cohort study. Lancet, 391, 451-461.	NR	NCT00468832	Study start: 2005-12 Study completion: 2019-12	No glucocorticoid treatment or cumulative treatment duration of less than 1 month versus treatment of 1 year or longer in male patients aged 2-28 years with Duchenne muscular dystrophy

Abbreviations: GC: Glucocorticoid

5.2 Literature used for the assessment of health-related quality of life

As the EPIDYS trial collected HRQoL data using PODCI and no mapping of EQ-5D was performed, a SLR was conducted to identify relevant published HRQoL evidence in patients with a diagnosis of DMD. Searches were conducted through May and June 2024 and updated in November 2024. The methodology undertaken is presented in detail in Appendix I. A total of 25 publications were included in the HRQoL SLR from the database searches, grey literature searches, and hand searching. Of the 25 identified studies, 12 collected HRQoL data using the EQ-5D. Of the 12 studies reporting EQ-5D data, five reported on patient HRQoL stratified by health state, five reported on patient HRQoL overall, and two studies reported on the same analysis of caregiver HRQoL which stratified utilities by health state. Audhya et al. 2023 informs patient utilities in the base case as it is best suited. The measurements align with the health states specified in the CEM and the methods for determining utilities align with guidelines i.e. the EQ-5D measure was used. Furthermore, the study improves accuracy and relevance by collecting data directly from the patients and not through the caregivers. This study is also the most recent patient HRQoL data available in DMD. Limitations associated with this study relate to the study being based in the US with utilities derived from the US tariff. Audhya et al. 2023, as well as the references used for disutilities due to spinal fusion surgery and adverse events are summarized in Table 11.

Table 11: Relevant literature included for (documentation of) health-related quality of life (See section 10)

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Audhya et al. (2023b). Estimating health state utilities in Duchenne muscular dystrophy using the health utilities index and EQ-5D-5L. Journal of patient-reported outcomes, 7(1), 132.	Health state utilities	Section 10.3

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Matza et al. (2014). Health state utilities for skeletal-related events secondary to bone metastases. The European journal of health economics: HEPAC : health economics in prevention and care, 15(1), 7–18.	Spinal fusion surgery disutility	Section 10.3
Sullivan et al. (2011). Catalogue of EQ-5D scores for the United Kingdom. *Medical decision making : an international journal of the Society for Medical Decision Making*, *31*(6), 800–804.	Diarrhoea adverse event disutility	Section 10.3
Hagiwara et al. (2018). Impact of Adverse Events on Health Utility and Health-Related Quality of Life in Patients Receiving First-Line Chemotherapy for Metastatic Breast Cancer: Results from the SELECT BC Study. PharmacoEconomics, 36(2), 215–223.	Vomiting (adverse event) disutility	Section 10.3

5.3 Literature used for inputs for the health economic model

A comprehensive SLR was conducted to identify all published evidence of the clinical efficacy, safety and tolerability of givinostat and ECM for DMD (section 5.1). The literature search is presented in detail in Appendix J. Due to lack of data on resources and disease management costs of DMD patients over the course of disease progression in Denmark, UK health state cost data from Landfeldt et al. (2017a) was used in the model. Landfeldt et al. (2017a) was identified in the SLR (Appendix J).

Table 12: Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Landfeldt et al. (2017a). Economic Evaluation in Duchenne Muscular Dystrophy: Model Frameworks for Cost-Effectiveness Analysis. Pharmacoeconomics, 35, 249-258.	Health state costs	Systematic literature review	Section 11.4
Rudolfsen et al. (2024). Burden of Disease of Duchenne Muscular Dystrophy in Denmark - A National Register-Based Study of Individuals with Duchenne Muscular Dystrophy and their Closest Relatives. J Neuromuscul Dis.	Proportion of patients with spinal fusion surgery in SoC	Targeted literature search	Section 11.8
McDonald et al. (2018). Long-term effects of glucocorticoids on function, quality of life, and survival in patients with Duchenne muscular dystrophy: a prospective cohort study. Lancet. 391:451-61	Time to spinal fusion surgery after loss of ambulation	Systematic literature review	Section 11.8

6. Efficacy

6.1 Efficacy of givinostat and GCs compared to placebo and GCs for the treatment of DMD

6.1.1 Relevant studies

6.1.1.1 EPIDYS

EPIDYS is a multicentre, randomised, double-blind, placebo-controlled, Phase 3 study (Mercuri et al. 2024b, Mercuri et al. 2024c). The study duration was planned for 19 months and was comprised of two phases (Mercuri et al. 2024c, Italfarmaco 2022a):

- Screening period: starting 4 weeks (±2 weeks) before randomisation. During the screening period, the 4SC test was to be performed at Visit 1 and 2
- Double-blinded treatment period: 18 months of treatment (72 weeks).

At the end of the study period, patients in both treatment arms had the opportunity to be included in the long-term extension study, OLE study (Study 51) to receive givinostat up to MA. A final follow-up visit was scheduled 4 weeks after the last dose of treatment received, if patients were not included in the , OLE (Study 51) (Italfarmaco SpA 2020).

The boys attended study site visits every 12 weeks for 18 months. At every visit, the boys completed a 4SC, the NSAA (including time-to-rise from the floor), a 6-minute walking test (6MWT) and muscle strength assessment (knee extension and elbow flexion, by standardised hand-held myometry) (Mercuri et al. 2024b, Mercuri et al. 2024c). All functional and strength assessments were evaluated by trained physiotherapists masked to treatment and other assessments, with all baseline and 72-week visits recorded and reviewed by an expert, independent team of physiotherapists, not otherwise involved in the study, for quality assurance (Mercuri et al. 2024b, Mercuri et al. 2024c). MRS of the right upper leg was done at after 48 and 72 weeks, with the images centrally read by an independent team of MRS experts, not otherwise involved in the study, for the calculation of VL MFF (Mercuri et al. 2024b, Mercuri et al. 2024c). Drug compliance was assessed using diary data (Mercuri et al. 2024b, Mercuri et al. 2024c).

A summary of the study design is shown in Figure 4 and the study is presented in detail in 0.

Figure 4: EPIDYS | Study design

Notes: Two MRI/MRS assessments occurred during the 72-week double-blind treatment period; *in addition to standard of care, including the use of GCs in the givinostat arm 20% and 80% of boys were treated with prednisone/other and deflazacort, respectively and in the placebo group arm, 23% and 77% of boys were treated with prednisone/other and deflazacort, respectively.

Abbreviations: BL: baseline; MRI: magnetic resonance imaging; MRS: magnetic resonance spectroscopy; n: number of patients in the study population; S: screening.
References: Mercuri et al. (2024b), Mercuri et al. (2024c), ClinicalTrials.gov (2023a).

6.1.1.2 OLE (Study 51)

The OLE study (Study 51, NCT03373968) is an ongoing multicentre, open-label, long-term study to assess the safety, tolerability, and efficacy of givinostat (ClinicalTrials.gov 2023b, Italfarmaco 2023, Italfarmaco 2024s). It includes boys with DMD previously enrolled in either Study 43 or EPIDYS, and also includes 30 givinostat-naïve patients with DMD (boys screened in EPIDYS who met all the inclusion criteria and none of the exclusion criteria but were not randomised because the enrolment in the off-target group was complete) (ClinicalTrials.gov 2023b). The study is presented in detail in appendix 0.

6.1.1.3 UK real-world data study

The aim of the UK real-world data study was to evaluate the effect of continuing GC treatment on pulmonary function in adults with DMD. Data was taken from the renowned UK North Star Database that collects real time data based on structured and standardized forms (Muscular Dystrophy UK 2025). As part of a natural history PhD study, a multicentre retrospective case note review was conducted between three UK hospitals (in London, Newcastle, and Oxford) representing approx. 40% of the patients in the UK. Patients were stratified into 3 groups: GC Naïve (taken GCs for 12 months or less), GC stopped (used GCs but stopped prior to transition to adult services) and GC continued (continued GCs into adulthood). Data was collected between February 2020 and July 2022 (Pietrusz et al. 2023).

The study population included adult patients with DMD aged 16 years and above with a diagnosis confirmed by genetic testing (Table 62) to exclude intermediate patients and other diagnoses. The study was a multicentre, retrospective, longitudinal, observational study conducted between three UK specialist neuromuscular centres (National Hospital

for Neurology and Neurosurgery (NHNN) in London, John Walton Muscular Dystrophy Research Centre in Newcastle, and John Radcliffe Hospital in Oxford).

Inclusion and exclusion criteria for the study can be found in appendix A.

The study included 209 patients across the three groups. Age at last assessment was 23.34 (SD 4.84), 21.29 (SD: 3.95) and 21.19 (SD: 2.76) in the CS Naïve (n=53), CS stopped (n=43), and CS continued (n=113) groups respectively. Data was collected on GC start age, GC stop age, GC treatment duration, ambulation status, age at LoA, NIV use, age at NIV start and, age at FVC <1L (Pietrusz et al. 2023).

Table 13: Overview of study design for studies included in the comparison

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
EPIDYS, NCT02851797 (Mercuri et al. 2024b)	Multicentre, randomised, double-blind, placebo-controlled, phase 3 trial	Study start: 2017-06-06 Study completion: 2022-02-22	179 male ambulant subjects were randomized 2:1 (givinostat: placebo) stratified by concomitant steroid use. Eligible participants were ambulant male patients aged at least 6 years with genetically confirmed Duchenne muscular dystrophy	Givinostat + GCs	Placebo + GCs	**Primary endpoint** Standard 4SC assessment (baseline and 18 months) **Secondary endpoints** • NSAA total score (baseline and 18 months) • NSAA cumulative loss of function (baseline and 18 months) • Time-to-rise from floor (baseline and 18 months) • Distance walked in 6 minutes (baseline and 18 months) • Muscle strength evaluated by knee extension (baseline and 18 months) • Muscle strength evaluated by elbow flexion measured by HHM (baseline and 18 months) • Mean change in VL MFF (baseline and 18 months) **Exploratory endpoint** PODCI (baseline and 18 months) **Safety endpoints** TEAEs, SAEs, mild TEAEs, moderate TEAEs and severe TEAEs (baseline and 18 months) Vital signs and clinical laboratory test results (blood chemistry and haematology) (baseline and 18 months) Respiratory function (baseline and 18 months) Cardiac function evaluated by ECG and echocardiogram (baseline and 18 months) Cognitive function (screening and at visit 18) Evaluation of acceptability/palatability of the oral suspension (week 4, 18 months and by potential early withdrawal)
OLE (Study 51), NCT03373968 (Italfarmaco 2024s)	Open-label, single arm long-term follow-up phase 2/3 study	Study Start: 2017-10-24	Patients who have participated in one of the previous studies	Givinostat + GCs (see Appendix A)	NA	**Primary endpoint (from week 48 until end of study)** Type, incidence, and severity of treatment-related/not related AEs and serious TEAEs (baseline, week 48 and yearly until end of study) **Secondary endpoints (ambulant patients)**

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
	(ongoing, enrolling by invitation)	Study completion (estimated): 2025-12	with givinostat in DMD. n = 207 enrolled at the fifth interim analysis cut-off date (31 Dec 2023)			• Physical functions, including 6MWD, NSAA, and Time function tests, such as TRF, 4SC, 4SC velocity, and 10MWT (Week 48 and then yearly until the end of study) • Muscle strength assessment, focusing on knee extension and elbow flexion, measured by HHM (Week 48 and then yearly until the end of study) **Secondary endpoints (non-ambulant patients)** • Physical function assessment using the EK score • Evaluation of activities of daily living through patient and caregiver reports, measured by the Barthel Index **Secondary endpoints (all patients)** • Physical function as measured by the PUL and MFM • Respiratory function evaluation, including FVC, FEV1, and PEF • Patient and caregiver QoL assessment, utilizing the PedsQL for paediatric patients and the SF-36 for adult patients • Monitoring age-related milestones in the disease progression, including age at LoA, age at the need for respiratory support during the day, age at scoliosis surgery, and age at death **Exploratory endpoints (all patients)** • Physical function as measured by the PUL • Mean change of MFM • Respiratory function evaluation, including FVC, FEV1, and PEF • Monitoring age-related milestones in the disease progression, including age at LoA, age at the need for respiratory support during the day, age at scoliosis surgery, and age at death **Exploratory endpoints (ambulant patients)** • Physical functions including 6MWD and NSAA, and Time function tests such as TRF, 4SC and 10MWT • Muscle strength assessment, focusing on knee extension and elbow flexion, measured by HHM

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
						Exploratory endpoints (non-ambulant patients) • Mean change in the EK score • Evaluation of activities of daily living through patient and caregiver reports, measured by the Barthel Index • Muscle strength assessment, focusing on elbow flexion, measured by HHM **PKs endpoints** Analysis of population PK models to continue assessing givinostat in DMD patients
UK real-world data study, NA (Pietrusz et al. 2023, Pietrusz 2024, Pietrusz 2025)	A multicentre retrospective case note review	Data was collected between February 2020 and July 2022	Adults with DMD	GCs	NA	**Primary endpoints** • LoA • NIV • FVC Participants had assessments at baseline and Months 3, 6, 9, and 12 (ambulatory), or Months 6 and 12 (non-ambulatory). Long-term follow-up visits were at Months 18, 24, and annually thereafter.

Abbreviations: 4SC: 4-stair climb; 6MWT: 6-minute walking test; ECG: electrocardiogram; EK: Egen Klassifikation; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; GGT: gamma glutamyl transpeptidase; HHM: hand-held myometry; MFF: muscle fat fraction; MR: magnetic resonance; MRS: magnetic resonance spectroscopy; NIV: Non-invasive ventilation; NSAA: North Star Ambulatory Assessment; PEF: peak expiratory flow; PODCI: Paediatric Outcomes Data Collection Instrument; PUL: Performance of the Upper Limb; TTRF: time to rise from the floor; VL: vastus lateralis.

6.1.2 Comparability of studies

The clinical evidence supporting givinostat is based on two studies: the EPIDYS trial, RCT comparing givinostat to SoC, and an open-label extension (OLE) study (Mercuri et al. 2024b, Italfarmaco 2023). The objective of the relative efficacy analysis presented in Section 7 was to evaluate the relative effects of givinostat on long-term outcomes (e.g. ambulatory function), by comparing age at disease milestones between givinostat and SoC. In the absence of a control group beyond the 18th Months (EPIDYS duration) period, an external SoC cohort from a multicenter retrospective RWE study conducted in the UK was used to provide a comparator for the OLE data (Pietrusz et al. 2023, Pietrusz 2024). The study was based on prospectively collected data from the DMD North Star Database (Muscular Dystrophy UK 2025). This study was selected as it included the most recently collected data of European DMD patients, making it a representative source of contemporary real-world data, and was granular enough to allow for a matched adjusted indirect comparison (MAIC). Furthermore, DMD patient populations in the UK and Nordic countries are comparable in terms of clinical characteristics, follow standardized international treatment guidelines, and exhibit similar disease progression and milestone outcomes (Italfarmaco 2024e).

Of note, the givinostat studies were prospective studies performed on young ambulant children (some of them losing ambulation during the trial), whereas the study by *Pietrusz et al*. was retrospective in design (although based on prospectively collected data). As such, at face value, the patient populations in the givinostat trials and the SoC study differ on some parameters. However, the study by *Pietrusz et al.* is relevant for the comparison as it represents the course of the disease – measured in disease milestones – in a European setting with modern SoC, including early onset treatment with GCs with a majority of patients continuing treatment into adulthood (Italfarmaco 2024e).

6.1.2.1 Comparability of patients across studies

Baseline characteristics for the givinostat and SoC studies are provided in Table 14. Baseline data on type of GC, dose, and GC regimen for the SoC study is available in Appendix C. As the studies differ in study design (prospective vs. retrospective), some of the parameters are for natural reasons not comparable (e.g. age and timed functional tests). In order to adjust for differences between the populations, the GC naïve subpopulation in the Pietrusz et al. (2023) study was excluded in the MAIC, and the data adjusted for age at GC start age (see Section 7).

Table 14: Baseline characteristics of studies included in the indirect treatment comparison

	EPIDYS Study 48	OLE Study 51	Pooled EPIDYS/ OLE	UK real-world data (retrospektive)		Pooled UK real-world data
Treatment	Givinostat	Givinostat	Combined, givinostat	GCs Stopped	GCs continued	Combined GCs (standard of care)
N	118	30	148	43	113	156
Age (years)						

	EPIDYS Study 48	OLE Study 51	Pooled EPIDYS/ OLE	UK real-world data (retrospektive)		Pooled UK real-world data
Mean (SD)	9.78 (2.02)	10.5 (2.25)	9.92	21.29	21.19	NR
Range	6.30 to 15.9	6.10 to 14.4	6.10 to 15.9	16 – 35.67	16.92 – 29.17	NR
GCs start age (years)						
Mean (SD)	6.11 (1.74)	6.03 (2.37)	6.09 (1.88)	7.19 (1.73)	7.20 (1.96)	7.20 (1.90)
Range	3.12 to 12.6	1.38 to 10.9	1.38 to 12.6	4 to 11.5	4 to 12.42	4 to 12.42
Race, n (%)						
White	106 (89.8)	22 (73.3)	128 (86.5)	NR	NR	NR
Asian	4 (3.4)	2 (6.7)	6 (4.1)	NR	NR	NR
Black/ African American	3 (2.5)	1 (3.3)	4 (2.7)	NR	NR	NR
Other	5 (4.2)	5 (16.7)	10 (6.8)	NR	NR	NR
BMI (kg/m²)						
Mean (SD)	19.7 (4.10)	20.2 (4.04)	19.8 (4.08)	NR	NR	NR
Range	12.4 to 30.6	13.9 to 30.5	12.4 to 30.6	NR	NR	NR
Time since first GCs initiation (years)						
Mean (SD)	3.62 (2.09)	4.47 (2.65)	3.80 (2.23)	NR	NR	NR
Range	0.43 to 8.88	0.91 to 12.6	0.43 to 12.6	NR	NR	NR
Use of GC at baseline, n (%)						
Deflazacort	91 (77.1)	27 (90.0)	118 (79.7)	NR	NR	NR
Other steroid	27 (22.9)	3 (10.0)	30 (20.3)	NR	NR	NR
Time to rise from floor (sec)						
Mean (SD)	6.89 (7.43)	5.57 (2.06)	6.62 (6.71)	NR	NR	NR
Range	2.60 to 60.2	3.00 to 9.50	2.60 to 60.2	NR	NR	NR
Time to 4SC (sec)						
Mean (SD)	3.58 (1.25)	3.58 (1.28)	3.58 (1.25)	NR	NR	NR
Range	1.80 to 7.10	1.80 to 6.60	1.80 to 7.10	NR	NR	NR
Time to walk/run 10 metres						
Mean (SD)	5.56 (1.34)	19.0 (74.6)	8.28 (33.6)	NR	NR	NR
Range	3.50 to 9.50	3.20 to 414	3.20 to 414	NR	NR	NR

Abbreviations: 4SC: 4-stair climb; BMI: body mass index; NR: not reported; OLE: open-label extension; SD: standard deviation; sec: second.

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

The study population in EPIDYS & OLE studies (Italfarmaco 2022a) and the control data set used in the estimation of relative efficacy (the UK RWE study) (Pietrusz et al. 2023) ,

similar to that in the Danish DMD population with respect to the age at diagnosis, disease progression, and the standard of care offered, including age at initiation of GC treatment (Italfarmaco 2024c). In the health economic model, the patients enter the model in the early ambulatory stage at age 6, which is representative of the long-term steady-state incident population. The relevant parameter used in the model is body weight, as this is used for calculation of the givinostat dose (European Medicines Agency 2025). In the model, Danish growth charts are used to estimate body weight by patient age (Sundhed.dk 2025, SDU.dk 2025).

Table 15: Characteristics in the relevant Danish population and in the health economic model*

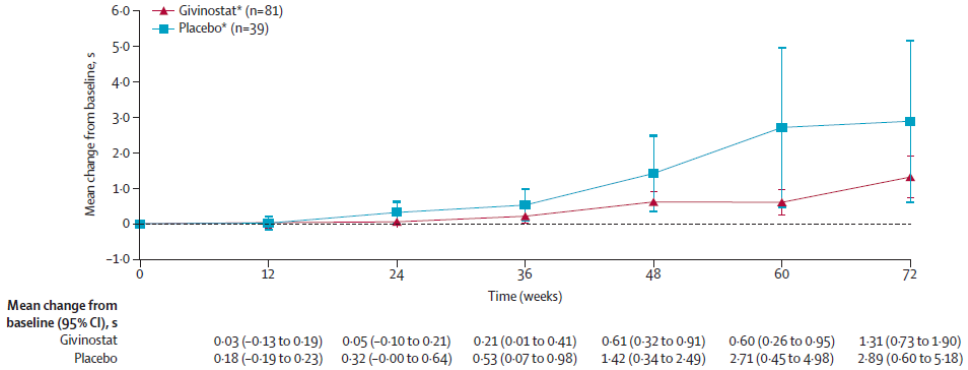
	Value in Danish population (reference)	Value used in health economic model (reference if relevant)
Age	6 years	6 years
Gender	100%	100% male
Patient weight	Assumed to follow weight by age curves for the general Danish population	21.75 kg at age 6; 86.4 kg at age 18+ based on Danish growth charts
Disease stage	100% early ambulatory	100% early ambulatory

*Validated by Danish KOL (Italfarmaco 2024c)

6.1.4 Efficacy – EPIDYS | Primary endpoint | Change in 4SC | Target ITT population

The EPIDYS trial successfully met its primary endpoint, demonstrating a meaningful and statistically significant difference in the mean change in time to climb 4SC at 18 months. A treatment effect of 0.86 was observed (p=0.035), confirming the primary analysis outcome. The pre-specified geometric LS mean ratios for the log transformed 4SC results at 18 months versus baseline were 1.27 (95% CI 1.17 to 1.37) in the givinostat group versus 1.48 (95% CI 1.32 to 1.66) in the placebo group (ratio 0.86; 95% CI 0.75 to 0.99, p=0.035; Figure 7 and Table 64 in Appendix 0) (Mercuri et al. 2024b, Mercuri et al. 2024c).The greater worsening in 4SC results with placebo than with givinostat was apparent from Week 48 (mean changes from baseline: givinostat, ranging between 0.60 and 1.31 seconds; placebo, 1.42 to 2.89 seconds**;** Figure 5). Non-log-transformed data showed a reduction of ~40% in the decline in 4SC over 18 months for givinostat vs. placebo (Appendix 0). When analysed as velocity, 4SC results at 18 months were 0.243 tasks per second in the givinostat group and 0.209 tasks per second in the placebo group, a LS mean difference of 0.034 (95% CI 0.004 to 0.065) tasks per second (p=0.029) (Mercuri et al. 2024b, Mercuri et al. 2024c).

Figure 5: Mean change of the 4SC assessment between baseline and 18 months | Target ITT population



Note: Data are mean (95% CI); the CIs have not been adjusted for multiplicity and should not be used for hypothesis testing; baseline mean values were 3.39 seconds for the givinostat group and 3.48 seconds for the placebo group; *all boys were also receiving systemic GCs, in a dose and regimen that was to remain unchanged over the follow-up period.
Abbreviations: 4SC: 4-stair climb; CI: confidence interval; ITT: intention-to-treat; LS: least squares; n: number; s: seconds.

Source: Mercuri et al. (2024b), Mercuri et al. (2024c)

These results are clinically meaningful. A recent publication has shown that 4SC >6.2 seconds is predictive of loss of function in the following year (Arora et al. 2018). A slower 4SC correlates with reduced participation in physical and social activities in daily life and predicts loss of stair-climbing ability and ambulatory capacity (Bushby and Connor 2011). At the end of EPIDYS, 12.3% of boys had a 4SC >6.2 seconds in the givinostat group compared with 26.5% in the placebo group. Moreover, the velocity difference between the givinostat and placebo groups of 0.034 tasks per second (Mercuri et al. 2024b, Mercuri et al. 2024c) is similar to the minimal clinically important difference reported by Duong and colleagues (0.035 tasks per second; derived using a questionnaire-anchored approach) (Duong et al. 2021).

Data presented at the Muscular Dystrophy Association (MDA)conference 2025, shows the off-target population (group B in the EPIDYS study) are generally consistent with those observed in the ITT and target populations, suggesting that givinostat is effective across a range of disease courses, as measured by VLFF (including ≤5% and >30%). All patients with DMD, including those with less severe and more severe disease progression, could have the potential for treatment benefits with givinostat (Finkel et al. 2025).

Additional analyses of the primary outcome are described in Appendix 0.

6.1.5 Efficacy – EPIDYS | Key secondary endpoints | Target ITT population

All key secondary endpoints favoured givinostat vs control. Givinostat slowed the decline in functional outcomes relating to daily activities, slowed decline in muscle strength, and slowed fat fraction infiltration in the leg muscles at 18 months compared with SoC. Givinostat also showed numerically less decline in NSAA total score than with placebo, at 18 months (least squares [LS] mean difference 1.9; 95% confidence interval [CI] 0.3 to

3.5; nominal p=0.021). Boys receiving givinostat were more likely to be still able to run, jump, hop and rise from a chair at 18 months than those who received placebo.

Givinostat treatment was associated with 40% less decline in cumulative loss of NSAA items. Cumulative loss of function was numerically lower with givinostat than with placebo, (2.14 fewer items failed over 18 months; nominal p=0.0202); This is important because a loss of 2.0 NSAA items predicts clinically meaningful disease progression and loss of ambulation in a functionally declining group (McDonald et al. 2022a). Muscle strength, evaluated by knee extension or elbow flexion (and normalised by subject weight; N/kg), showed numerically less decline with givinostat than with placebo at 18 months.

Treatment with givinostat reduced fat infiltration in VL muscle versus placebo by approximately 30% (LS mean difference for givinostat-placebo: –2.9%; nominal p=0.035). This is considered to be clinically meaningful, because increased VL MFF inversely correlates with muscle function, daily activity (4SC and time to rise from the floor [TTRF]) and predicts loss of ambulation (Barnard et al. 2020).

Overall, reductions in the rate of decline in ambulatory ability seen in EPIDYS are strongly suggestive of a delay in the loss of ambulation for boys with DMD and are expected to delay disease progression more generally as patients' DMD progresses. Analyses of the EPIDYS key secondary outcomes are described in Appendix 0.

6.1.6 Efficacy – OLE study | longer-term givinostat efficacy at the December 2023 data cut-off | Overall ITT population

The OLE study included three givinostat treatment subgroups – due to limited event outcomes at the current data cut, we have presented pooled data for the Overall givinostat population.

No formal hypothesis testing was planned for the secondary efficacy endpoints. When interpreting the efficacy and PedsQL scores results, it is important to note that there were a number of missing values, mainly due to visits not being performed at the site due to the COVID-19 pandemic (Italfarmaco 2024s). Missing values due to LoA or inability to perform the test or cases for which a clear reason for not performing the tests was not reported were imputed as Class 2 data. This led to some missing values imputed to a penalising value, meaning that the analyses reported in Appendix F are conservative (Italfarmaco 2024s).

6.1.6.1 Ambulation status

In the Overall ITT population [redacted] ambulant and [redacted] non-ambulant at baseline), 78 (37.7%) young men had lost ambulation by the December 2023 DCO; the median age at LoA was 18.1 years (95% CI [redacted]) for the patients treated with givinostat from study entry (Italfarmaco 2024s, Italfarmaco 2025a). This is higher than the median age expected in a DMD population treated with GCs only (e.g. the estimated median age at loss of ambulation in a 2022 analysis of data from the UK North Star Network database

(Muscular Dystrophy UK 2025) was 11 years 8 months [interquartile range: 10 years 1 month–14 years 5 months]) (Zambon et al. 2022).

6.1.6.2 Lung function

By the December 2023 data-cut, pulmonary function tests showed a minimal increase from baseline for FVC and forced expiratory volume in 1 second (FEV1) until 4 years of treatment; while % predicted FVC showed a steady decrease throughout the study period, with a mean fall of 3.4% in the first year of treatment, and a mean fall of about 19.7% after 4 years of treatment. Peak expiratory flow (PEF) showed a steady increase throughout study and a minimal decrease of % predicted PEF with a mean value of −14.8% after 4 years of treatment (Italfarmaco 2024s).

Comparison of the % predicted FVC and PEF collected in this study with published data from natural history studies, suggests no negative effects of givinostat on respiratory function, and may suggest a slowing down of disease progression (Italfarmaco 2024s).

Two of the young men reached a need for daytime respiratory support during follow-up; note, both patients were previously treated in Study 43 (ClinicalTrials.gov 2023a).

Respiratory long term data comparison of patients that lost ambulation during OLE with the PRO-DMD-01 (NCT01753804) natural history study suggest improved stabilization of pulmonary function with givinostat treatment (McDonald et al. 2025).

6.1.7 Efficacy – SoC | Outcomes of the UK real-world data study

Results from the UK RWE study are presented in Appendix 0.

6.1.8 Additional studies

6.1.8.1 Study 43 (Phase I/II)

Study 43 is a two-part Phase I/II open-label study to assess safety and tolerability, PK and effects on histology, and different clinical parameters of Duvyzat® (givinostat) in ambulant patients from 7 years old to less than 11 years old with DMD. A total of 20 patients were included in the study (ClinicalTrials.gov 2023c, Bettica et al. 2016). A total of 20 patients were included in the study (ClinicalTrials.gov 2023c, Bettica et al. 2016). Study 43 is described in detail in Appendix N.

7. Comparative analyses of efficacy

The EPIDYS trial provides key milestone data for delay in disease progression for patients receiving givinostat in addition to SoC, compared with Soc without givinostat, across an

18-month follow-up. Over the follow-up period of the study, givinostat demonstrated meaningful benefits versus SoC. Following the completion of the pivotal trial EPIDYS, patients from the phase I/ II study and EPIDYS were invited to participate in an open-label extension study (OLE) to received givinostat in addition to SoC until MA. By definition, the open-label study is a single-arm study, meaning that all participants receive the investigational treatment, therefore the OLE (study 51) continues to collect long-term data specifically for givinostat with concomitant SoC.

To assess the long-term efficacy of givinostat versus the SoC beyond the 18th months (EPIDYS duration), on disease milestones in the absence of a control group, a UK RWE study was utilized as a comparator (Pietrusz et al. 2023, Pietrusz 2024). This approach allows for a more comprehensive evaluation of treatment effects by benchmarking outcomes against the progression observed in an untreated or conventionally managed patient population beyond the duration of the EPIDYs trial.

As the UK real-world data and the givinostat evidence do not have a common comparator, unanchored matching-adjusted indirect comparisons (MAICs) are utilised to derive the relative efficacy of givinostat versus SoC. The MAICs aim to evaluate the relative effects of givinostat on ambulatory and non-ambulatory function, by comparing age at disease milestones (e.g. age at LoA) between givinostat and SoC. These data are used to inform the relative efficacy in the CEM.

7.1.1 Differences in definitions of outcomes between studies

In the MAIC described in the following sections, the outcomes assessed were Age at LoA, Age at NIV, and Age at FVC<1L. The definitions of the outcomes are described in Table 8. In the UK Real World Data study used for the SoC arm (Pietrusz et al. 2023), the exact definitions are not described. However, the study extracted data from the DMD North Star Database, which employs a standardised data collection sheet with data collected every 6 months (Muscular Dystrophy UK 2025). The definitions for age at NIV and age at FVC<1L can thus be assumed to be the same as the ones used in the EPIDYS/OLE study. For age at LoA, there is a slight discrepancy. In EPIDYS/OLE, LoA is defined as satisfying both the following criteria at the same visit:

- Subject is unable to perform the 6MWT due to physical inability.
- Subject is unable to complete the 10MWT in 30 seconds or less without any support or devices (10-metre walk/run test grading ≤2).

In the North Star Database, however, LoA is defined as inability to walk 10 meters without assistance (i.e. no time cut-off).

In the comparative analysis, no adjustment was made for the difference in definitions for LoA between the studies. As the definition for LoA in EPIDYS/OLE is stricter than in the UK Real World Data study, it is possible that some patients in the SoC arm would be classified as ambulatory for a longer period of time than in the givinostat arm, as they may complete the 10MWT in >30 seconds. If that is the case, the comparative analysis is conservative. However, the decline in walking ability is steep, and patients not able to

complete the 10MWT in less than 30 seconds are likely to lose the ability to complete it at all in a short time period.

7.1.2 Method of synthesis

From the included studies, individual patient data (IPD) were available for patients receiving givinostat whilst aggregate-level data were available for those receiving SoC. Unanchored MAICs were performed for age at LoA, age at NIV and age at FVC <1L. Age at start of GC therapy was included as a matching variable in the MAIC. Acceleration factors were used to enable comparison from the available data, in addition to a population adjustment via the MAIC. More details on the method of synthesis are available in Appendix C. The MAIC analyses conducted are presented in Table 16 below.

Table 16: Matching adjusted indirect treatment comparisons conducted

Endpoint	Givinostat data	SoC data	AFT estimate	Matching variables
Age at loss of ambulation	Age at loss of ambulation KM	Age at NIV KM for GC stopped / GC continued applying AFT of 0.67 / 0.66, respectively	AFT estimated from median age at loss of ambulation for SoC / median age at NIV for SoC: GC stopped = 10.67/16 = **0.67** GC continued = 12.67/19.17 = **0.66**	GC start age (years)
Age at NIV	Age at loss of ambulation KM with AFT of 1.50	Age at NIV KM	AFT estimated from median age at NIV for SoC / median age at loss of ambulation for SoC: 18.46/12.28[†] = **1.50**	GC start age (years)
Age at FVC <1L	Age at loss of ambulation KM with AFT of 1.94	Age at FVC <1L KM	AFT estimated from median age at FVC <1L for SoC / median age at loss of ambulation for SoC: 23.86/12.28[†] = **1.94**	GC start age (years)

Note: [†]Estimates for SoC from combined GCs stopped and continued groups.
Abbreviations: 1L: one litre; AFT: acceleration factor; FVC: forced vital capacity; KM: Kaplan-Meier; NIV: non-invasive ventilation; SoC: standard of care

7.1.3 Results from the comparative analysis

The givinostat studies (unadjusted and weighted) and baseline characteristics for SoC for the conducted analyses in the base case are presented in Table 17. Matching was based on age at start of GCs treatment. The effective sample size (ESS) was 105.1, a reduction of around one-third smaller than the original sample size of 148 givinostat patients, suggesting reasonable overlap in patient characteristics for age at start of GCs treatment. Model diagnostics, including distribution of weights, are presented in Appendix C.

Table 17: Baseline characteristics: givinostat (EPIDYS and OLE Study) vs. SoC (UK real-world data)

Treatment arm	N/ESS	Glucocorticoids start age (years)
Givinostat unadjusted	148.0	6.09
Givinostat weighted	105.1	7.20
Standard of care	156.0	7.20

Abbreviations: ESS: effective sample size.

Results of the comparative analysis of givinostat vs SoC are presented in Table 18.

The unanchored MAIC analyses predict the following clinical events:

- A HR of 0.185 (95% CI: 0.121 – 0.282) for age at loss of ambulation for givinostat vs. SoC. The median for the unadjusted givinostat data is 17.97 (95% CI: 15.40 – not evaluable [NE]) and for the MAIC-weighted givinostat data is NE (95% CI: 15.52 – NE).
- A HR of 0.190 (95% CI: 0.124 – 0.290) for age at non-invasive ventilation for givinostat vs. SoC. The median for the unadjusted givinostat data is 27.00 (95% CI: 23.14 - NE) and for the MAIC-weighted givinostat data is NE (95% CI: 23.32 – NE).
- A HR of 0.214 (95% CI: 0.139 – 0.329) for age at FVC<1L for givinostat vs. SoC. The median age for the unadjusted givinostat data is 34.90 (95% CI: 29.91 - NE) and for the MAIC-weighted givinostat data is NE (95% CI: 30.14 – NE).

Table 18: Results from the comparative analysis of givinostat vs. SoC for patients with DMD

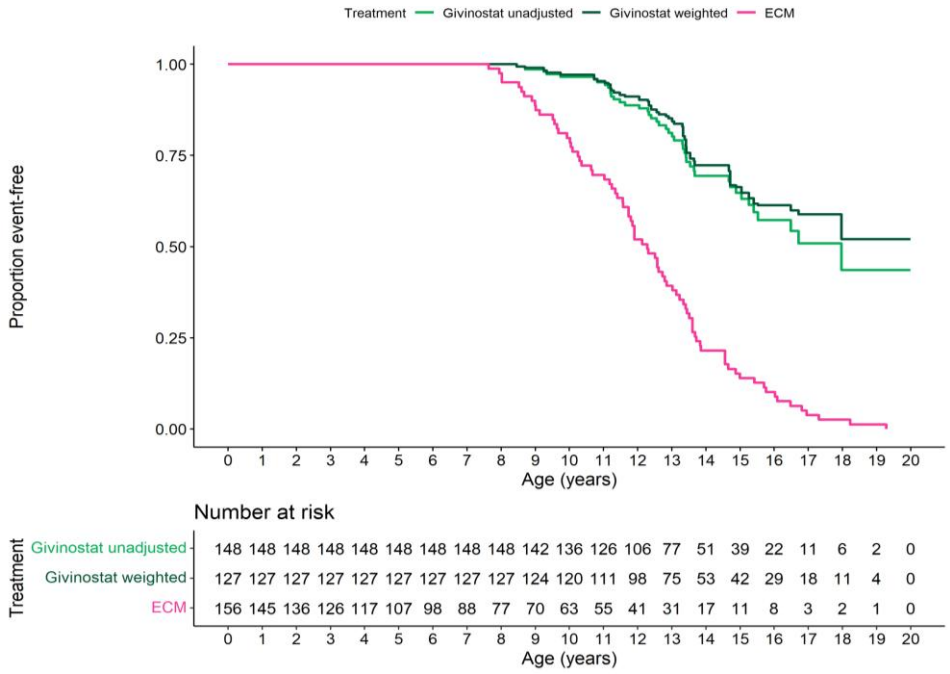
Outcome measure	Givinostat unadjusted (EPIDYS/OLE) (N=148)	Givinostat weighted (EPIDYS/OLE) (ESS=105.1)	SoC (UK Real-world data) (N=156)	Result Givinostat vs SoC, HR (95% CI)
Age at LoA, years (95% CI) [number of events]	17.97 (15.40, NE) [redacted]	NE (15.52, NE) [redacted]	12.28 (11.74, 13.13) [redacted]	Unadjusted: [redacted] Weighted (Robust SE): [redacted] Weighted (Bootstrap): [redacted]
Age at NIV, years (95% CI) [number of events]	27.00 (27.14, NE) [redacted]	NE (23.32, NE) [redacted]	18.46 (17.76, 19.70) [redacted]	Unadjusted: [redacted] Weighted (Robust SE): [redacted] Weighted (Bootstrap): [redacted]
Age at FVC <1L, years (95% CI) [number of events]	34.90 (29.91, NE) [redacted]	NE (30.14, NE) [redacted]	23.86 (21.62, 26.47) [redacted]	Unadjusted: [redacted] Weighted (Robust SE): [redacted] Weighted (Bootstrap): [redacted]

Note: Bold text indicates a significant difference between treatments.
Abbreviations: 1L: 1 litre; CI: confidence interval; DMD: Duchenne Muscular Dystrophy; ESS: effective sample size; FVC: forced vital capacity; HR: hazard ratio; MAIC: matching-adjusted indirect comparison; NE: not evaluable; SE: standard error, SoC: Standard of care.

7.1.4 Efficacy – results per Age at loss of ambulation

The KM plots for age at loss of ambulation for givinostat patients for both unadjusted and weighted patient data, compared with patients receiving SoC (estimated using an acceleration factor) are presented in Figure 6.

Figure 6: Kaplan-Meier plot for age at loss of ambulation MAIC: givinostat (EPIDYS and OLE study) vs. SoC/ECM (UK real-world data)



Abbreviations: ECM: Established Clinical Management, i.e. Standard of care; MAIC: matching-adjusted indirect comparison; OLE: open-label extension; SoC: standard of care; UK: United Kingdom.

Median age at LoA for givinostat treated patients[b] was 17.97 years pre-weighting and not reached post-weighting, compared with 12.28 years for SoC treated patients (Table 19). This estimate of age at loss of ambulation for patients receiving SoC was consistent with evidence from CINRG (Mercuri et al. 2023b, McDonald et al. 2018) and considered the most relevant estimate for the UK population. Furthermore, this estimate of loss of ambulation is also representative of Danish population, where loss of ambulation occurs at approximately [redacted](Italfarmaco 2024c) similar to data from Norway with 11.1 year ±2.1 and Sweden with 10.9 (Annexstad et al. 2019, Italfarmaco 2025b). The similarity on the result for loss of ambulation is not unexpected, as both countries follow similar treatment guidelines, and GCs remain the only available treatment option. Patients treated with givinostat were [redacted]at loss of ambulation compared with patients treated with SoC, with HR (95% CI) of [redacted]from

[b] The analysis is based on givinostat treated cohort from the EPIDYS study and patients from Study 43 that met the EPIDYS inclusion criteria at treatment start continuing in the OLE study

the weighted comparison with robust SE; these results were aligned with results from the bootstrap estimation (HR [95% CI] [redacted]

Table 19: Summary of age at loss of ambulation MAIC: givinostat (EPIDYS and OLE study) vs. SoC (UK real-world data)

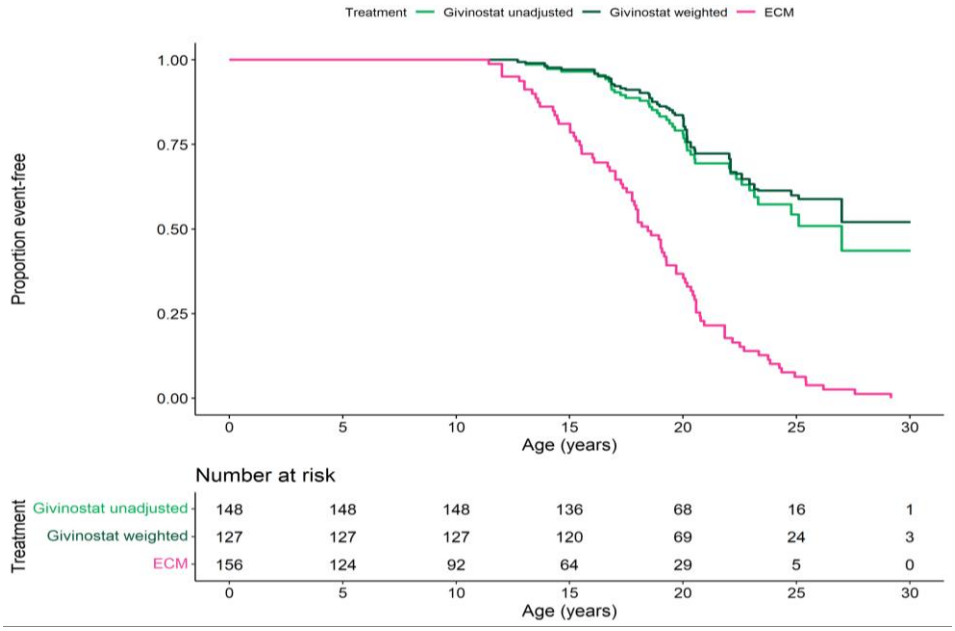
Treatment (study)	N/ESS	Events	Median (95% CI)	Givinostat vs. SoC HR (95% CI)
Givinostat unadjusted (EPIDYS/OLE)	148.0	43	17.97 (15.40, NE)	**0. 222 (0.153, 0.323)**
Givinostat weighted (EPIDYS/OLE)	105.1	36	NE (15.52, NE)	Robust SE: **0.185 (0.121, 0.282)** Bootstrap: **0.184 (0.127, 0.261)**
SoC (UK real-world data)	156.0	79	12.28 (11.74, 13.13)	Not applicable

Note: Bold text indicates a significant difference between treatments.
Abbreviations: CI: confidence interval; ESS: effective sample size; HR: hazard ratio; MAIC: matching-adjusted indirect comparison; NE: not evaluable; OLE: open-label extension; SE: standard error; SoC: standard of care.

7.1.5 Efficacy – results per Age at non-invasive ventilation

As noted previously, there were [redacted]events for age at NIV amongst the patients receiving givinostat during the study follow-up (see Figure 28). However, applying the estimated acceleration factor to the age at loss of ambulation data (Table 16), KM curves for estimated age at NIV for givinostat patients for the unadjusted and weighted patient data, compared with patients receiving SoC are presented in Figure 7.

Figure 7: Kaplan-Meier plot for age at NIV MAIC: givinostat (EPIDYS and OLE study) vs. SoC (UK real-world data)



Abbreviations: ECM: Established Clinical Management, i.e. Standard of care; MAIC: matching-adjusted indirect comparison; NIV: non-invasive ventilation; SoC: standard of care; UK: United Kingdom.

Median age at NIV for givinostat treated patients was 27.0 years pre-weighting and not reached post-weighting, compared with 18.5 years for SoC treated patients (Table 20).

Patients treated with givinostat were significantly older when receiving NIV, compared with patients treated with SoC with a HR (95% CI) of [redacted] from the weighted comparison with robust SE; these results were aligned with the results of the bootstrap estimation (HR [95% CI] [redacted]; Table 20).

Table 20: Summary of age at NIV MAIC: givinostat (EPIDYS and OLE study) vs. SoC (UK RWD)

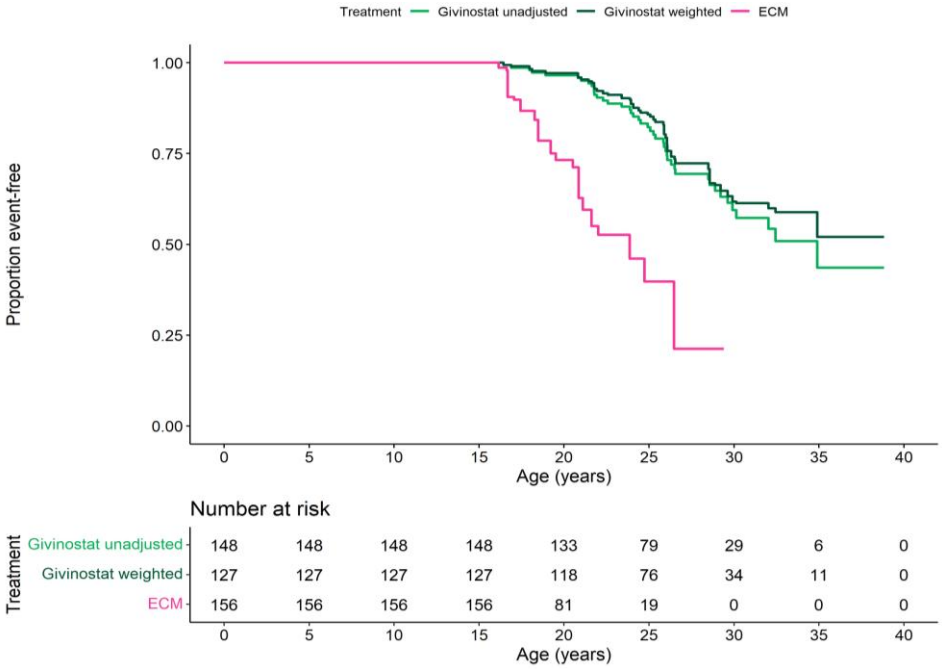
Treatment (study)	N/ESS	Events	Median (95% CI)	Givinostat vs. SoC HR (95% CI)
Givinostat unadjusted (EPIDYS/OLE)	148.0	43	27.00 (27.14 to NA)	**0.228 (0.157, 0.332)**
Givinostat weighted (EPIDYS/OLE)	105.1	36	NA (23.32 to NA)	Robust SE: **0.190 (0.124, 0.290)** Bootstrap: **0.191 (0.130, 0.264)**
SoC (UK real-world data)	156.0	79	18.46 (17.76 to 19.70)	Not applicable

Note: Bold text indicates a significant difference between treatments.
Abbreviations: CI: confidence interval; ESS, effective sample size; HR: hazard ratio; MAIC: matching-adjusted indirect comparison; NE: not evaluable; NIV: non-invasive ventilation; OLE: open-label extension; SE: standard error; SoC: standard of care.

7.1.6 Efficacy – results per Age at forced vital capacity <1L

As with age at NIV, there were zero events for FVC <1L amongst the patients receiving givinostat during the EPIDYS study follow-up. However, applying the estimated acceleration factor to the age at loss of ambulation data, KM curves for estimated age at FVC <1L for givinostat patients for the unadjusted and weighted patient data, compared with patients receiving SoC are presented in Figure 8.

Figure 8: Kaplan-Meier plot for age at FVC <1L MAIC: givinostat (EPIDYS and OLE study) vs. SoC/ECM (UK real-world data)



Abbreviations: 1L: 1 litre; ECM: Established Clinical Management, i.e. Standard of care SoC; FVC: forced vital capacity; MAIC: matching-adjusted indirect comparison

Median age at FVC <1L for givinostat treated patients was 34.9 years pre-weighting and not reached post-weighting, compared with 23.9 years for SoC treated patients (Table 21). Patients treated with givinostat were significantly older when reaching FVC <1L compared with patients treated with SoC with a HR (95% CI) of 0.21 (0.14, 0.33) from the weighted comparison with robust SE; these results were aligned with the results of the bootstrap estimation (HR [95% CI] 0.21 [0.15, 0.29]; Table 21).

Table 21: Summary of age at FVC <1L MAIC: givinostat (EPIDYS and OLE study) vs. SoC (UK real-world data)

Treatment (study)	N/ESS	Events	Median (95% CI)	Givinostat vs. SoC HR (95% CI)
Givinostat unadjusted (EPIDYS/OLE)	148.0	43	34.90 (29.91, NA)	**0.233 (0.154, 0.353)**
Givinostat weighted (EPIDYS/OLE)	105.1	36	NA (30.14, NA)	Robust SE: **0.214 (0.139, 0.329)** Bootstrap: **0.214 (0.151, 0.288)**
SoC (UK real-world data)	156.0	67	23.86 (21.62, 26.47)	Not applicable

Note: Bold text indicates a significant difference between treatments.
Abbreviations: 1L: 1 litre; CI: confidence interval; ESS: effective sample size; FVC: forced vital capacity; HR: hazard ratio; MAIC: matching-adjusted indirect comparison; NE: not evaluable; OLE: open-label extension; SE: standard error; SoC: standard of care.

8. Modelling of efficacy in the health economic analysis

8.1 Presentation of efficacy data from the clinical documentation used in the model

Natural history

The primary data source informing the Natural History Model (representing the current Danish SoC), developed by PH (Broomfield et al. 2024), is the C-Path D-RSC database, which includes anonymized individual patient data from 11 international data sources, including NH studies, placebo arms of clinical trials, and registry data (Broomfield et al. 2024). Please see Broomfield et al 2024 for description of NHM (Broomfield et al. 2024).

No mortality data were available from the D-RSC dataset (D-RSC 2025). Therefore, to inform the NHM mortality, a SLR and meta-analysis were performed by Broomfield et al. (2021). Kaplan Meier curves from 14 studies were digitized and IPD was reconstructed via a frequently used algorithm, details of which are presented by Guyot et al. (2012). This is a commonly used technique for obtaining IPD from published studies that make use of the fact that event times can be determined from the step function of a KM curve. The digitized mortality data contained 2,283 patients and 1,050 deaths across the 14 studies. The total follow-up time was 40,274 patient-years; the oldest patient in the dataset was aged 44 years. Mortality rates were determined from a parametric survival model assuming a piecewise constant hazard function. This included all 14 studies controlled for birth cohort (before 1970, 1970–1990, and after 1990) (Broomfield et al. 2024, Broomfield et al. 2023b, Broomfield et al. 2021).

Previous studies have observed improvements in survival since 1990 among individuals with DMD who are ventilated. The NHM authors observed this trend in the studies identified, with lower rates of mortality by age estimated in studies published since 1990. Therefore, mortality rates from the birth cohort after 1990 were used in the base-case analysis. The sub-set of patients born after 1990 included 943 patients, of whom 251 had died. Estimated median survival and reported statistics were consistent with the original studies. This validated the IPD reconstruction and estimation of mortality rates which were used in the NHM (Broomfield et al. 2024).

As described in section 8.1.1 below, the original NHM has been updated incorporating feedback from clinical experts and the NICE assessment of vamorolone stating that the original NHM overestimated survival.

No data from the EPIDYS control arm has been directly considered in the CEM, the main reason is that EIDYS trial started at an earlier age, and the trial endpoints consisted in prognostics factor of disease progression, and disease milestones such as LoA, but not LoA or respiratory function itself. Only 1 patient lost the ability to rise from the floor during the study, and therefore the time to loss of standing could not be evaluated and

only 1 patient lost ambulation during the study. Hence there wasn't enough data to inform transition probabilities of the cost-effectiveness comparator arm (clinical management without givinostat - SoC), and data from natural history was required to inform the SoC arm transition probabilities in the cost-effectiveness model. Please refer to section 3.7.1.1 for further explanation.

EPIDYS data is relevant because it shows statistically and clinically meaningful improvements in functional endpoints relevant to early disease progression, offering high-quality short-term data and supporting the extrapolations used in the indirect treatment comparisons and the predictions of the economic model.

Cardiomyopathy

The effect of cardiomyopathy on mortality is not modelled, as it is assumed that these effects are captured implicitly in the mortality rates for each health state. According to expert opinion, the incidence of cardiomyopathy in a particular health state of the disease and its duration is highly unpredictable. Moreover, the data available on cardiomyopathy is highly heterogeneous and patients can be asymptomatic for any stage of the disease. Therefore, due to the lack of data on the incidence, the heterogenous treatment regimens for cardiomyopathy, and to avoid double counting of the costs of "asymptomatic" cardiomyopathy, cardiomyopathy is not considered in the model.

Relative efficacy of givinostat

The relative efficacy of givinostat in addition to SoC vs. SoC alone has been estimated through unanchored MAICs (see Section 7) using data from the EPIDYS and the OLE (N=148) for givinostat matched to align with UK real-world data for SoC which has been validated to be similar to the Danish patient population (Italfarmaco 2024c).

The unanchored MAICs are based on outcomes measured from baseline. However, the CEM applies HRs to transitions between the health states. For example, the probability of losing ambulation in the CEM is based on a combination of the probability of progressing from health state (1) to (2), the probability of progressing from health state (2) to (3), and the probability of progressing from health state (3) to (4), as well as the probability of death from any of these ambulatory health states. Therefore, the CEM uses the data estimated by the MAICs and applies necessary assumptions to fit these outcomes to the granularity of the CEM.

Owing to the multiple transitions modelled within each endpoint, the HRs estimated by the MAICs cannot be applied directly within the CEM structure. Therefore, independent parametric curves were fitted to the MAIC-weighted givinostat data to estimate median values for age at loss of ambulation, age at non-invasive ventilation, and age at FVC<1L. Note: median values were not estimable from the MAIC-weighted givinostat Kaplan-Meier data. The CEM then used SOLVER to estimate the HRs relevant to transitions from:

- Health states (1) to (2), (2) to (3), and (3) to (4), such that the predicted median age at loss of ambulation from the CEM aligned with the best fitting curve from the parametric curves fit to the MAIC-weighted givinostat loss of ambulation data.

- Health states (4) to (5), (4) to (6), and (5) to (7a), such that the predicted median age at ventilation from the MAIC-weighted givinostat loss of ambulation data.
- Health states (4) to (5), (4) to (6), and (5) to (7a), such that the predicted median age at ventilation from the CEM aligned with the best fitting curve from the parametric curves fit to the MAIC-weighted givinostat non-invasive ventilation data.
- Health states (6) to (7b), (7a) to (8a), and (7b) to (8b), such that the predicted median age at FVC<30% from the CEM aligned with the best fitting curve from the parametric curves fit to the MAIC-weighted givinostat FVC<1L data.

As per the clinical advice provided to the External Assessment Group in the NICE submission for ataluren, it is considered reasonable to assume that FVC<1L is equivalent to FVC<30% i.e. aligning with health states (8a) and (8b) in the CEM (NICE 2023a) and Figure 8 in Section 7.1.4–7.1.6 present the MAIC-weighted givinostat data for loss of ambulation, non-invasive ventilation, and FVC<1L outcomes, respectively. Figure 50, Figure 51, and Figure 52 present the hazards underpinning the MAIC-weighted Kaplan-Meier plots. Note: due to the assumptions required in the MAICs, the hazard profile is the same shape for all outcomes see Section 0 (Appendix). As would be expected with the progression profile of DMD, the hazards of an event are shown to steadily increase over time.

8.1.1 Extrapolation of efficacy data

8.1.1.1 Extrapolation of survival for the natural history

A summary of assumptions regarding survival extrapolation for the natural history is described in Table 22. Survival data were only extrapolated to model the natural history. Givinostat was assumed to be associated with HR of one, thus having the same transition probabilities as SoC. Survival was based on the original published NHM which was later updated as described in this section further below. All information to fully populate the table below, such as fit statistics, was not available from the published material.

Table 22: Summary of assumptions associated with extrapolation of survival in natural history

Method/approach	Description/assumption
Data input	C-Path D-RSC database (natural history)
Model	Parametric model
Assumption of proportional hazards between intervention and comparator	Yes
Function with best AIC fit	Not available. Original NHM described by Broomfield et al. (2024)
Function with best BIC fit	Not available. Original NHM described by Broomfield et al. (2024)
Function with best visual fit	Not available. Original NHM described by Broomfield et al. (2024)
Function with best fit according to evaluation of smoothed hazard assumptions	Not available. Original NHM described by Broomfield et al. (2024)
Validation of selected extrapolated curves (external evidence)	The updated NHM was validated with real-world data and expert opinion

Method/approach	Description/assumption
Function with the best fit according to external evidence	Not available. Original NHM described by Broomfield et al. (2024)
Selected parametric function in base case analysis	Exponential
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	No (not applicable)
Assumptions of waning effect	No (not applicable)
Assumptions of cure point	No

Abbreviations: NHM: Natural history model

The published NHM provides a set of transition intensities to inform the natural history of DMD in economic evaluations of new treatments, where previously there has been a lack of data to inform health state transitions over the lifetime of patients. Additionally, the published NHM has been developed with input from patients, caregivers, and clinicians, which means that the health states reflect clinically important changes in patient care and HRQoL. However, there are limitations associated with the steps taken to overcome the paucity of data in the published NHM – as discussed in Broomfield et al. (2024). Notably, sparse data meant that the exponential distribution was used to fit the multi-state model, initially across all health states. However, its use resulted in clinically implausible mean durations in health states (8a) and (8b). Therefore, a piecewise exponential was assumed for transitions out of these health states to death, which was found to partly address this issue. However, the mean ages in health states (8a) and (8b) predicted by the published NHM are still higher than expected given the C-PATH D-RSC data – as reported in the publication – and real-world expectations.

Additionally, in the NICE appraisal of vamorolone for treating DMD (GID-TA11135) (NICE 2025), the clinical experts and the committee concluded that the median survival expected for patients with DMD from the literature was less than predicted by the published NHM.

Table 23 (also illustrated in Figure 39 in Appendix 0) compare the survival over time predicted by the different sources discussed in this submission. The predicted survival from the published NHM is shown to be higher than all alternative sources. Importantly, all external data sources indicate similar survival over time.

Table 23: A comparison of survival from the published NHM with the literature, UK real-world data, and clinician feedback

	Published NHM	Broomfield 2021	Broomfield 2023	Clinical feedback 2024	UK real-world data (stopped GCs)	UK real-world data (continued GCs)	Weighted UK real-world data
Median	35.58	21.83	25.37	NA	25.50	28.95	27.85
% surviving at (age):							
10	100%	100%	100%	100%	100%	100%	100%

20	90%	61%	76%	88%	97%	97%	97%
30	70%	26%	35%	45%	30%	7%**	15%
40	38%	14%	15%	12%	1%*	NA	5%
50	19%	7%	6%	3%	NA	NA	NA

Abbreviations: GCs: glucocorticoids; NA: not available; NHM: natural history model

Note: *% surviving based on last available data point at age 38. **% surviving based on last available data point at age 29.

In line with the discussion in Broomfield et al. (2024) surrounding the over-estimation in survival stemming from the final health states, NHM was updated to align the model and current real-world data. The analysis explored the potential of overestimation of transition probabilities in the published NHM in the earlier disease pathway. The original published NHM estimates that the median age of loss of ambulation is 15.5 years. However, RWD from Norway and Sweden suggests that, in clinical practice, patients lose their ambulation earlier with an average age at LoA of 11.1 years (SD: 2.1) and 10.9 years (Italfarmaco 2025b, Annexstad et al. 2019). Therefore, the updated NHM estimated two sets of hazard ratios using the SOLVER functionality: first the hazard ratio applied to transitions from health states (1) to (2), (2) to (3), and (3) to (4) and second the hazard ratio applied to transitions from health states (8a) and (8b) to death to align the median age at loss of ambulation with the unpublished UK real-world data and to ensure the proportion surviving at 50-years aligned with 2.8%. This returned a hazard ratio of **** for transitions from (1) to (2), (2) to (3), and (3) to (4) and **** for transitions from health states (8a) and (8b) to death. Table 24 (also illustrated in Figure 40 in Appendix 0) compares the predicted survival estimated from the updated NHM with the external sources and the published NHM. The updated NHM is shown to closely align with published and unpublished survival data, as well as with the UK clinician feedback (Figure 26). This is in line with the RWD from Norway mentioned above and was also confirmed by Danish clinician to be similar in Denmark (Italfarmaco 2024c). In a Danish study the mean age at death was DMD 26.8 years (IQR: 19–34) (Rudolfsen et al. 2024). Older patients were most likely diagnosed without genetic testing which increases the risk of misdiagnosis. Those patients are reflected in the tail of the survival curve in the updated NHM.

As an additional check for clinical plausibility, the per cycle rate of death was compared to the mortality rate in the general population matched for gender and age in each cycle in the CEM, using Danish mortality rates from Medicinrådet (2024). If the matched general population rate was higher, this was used in the CEM for that cycle. Note: background mortality only impacts transitions to death from health state (1).

Table 24: A comparison of survival from the updated NHM with external sources and the published NHM

	Updated NHM	Published NHM	Broomfield 2021	Broomfield 2023	Clinical feedback	UK real-world data (continued GCS)	Weighted UK real-world data
Median	****	35.6	21.8	25.4	NA	28.9	27.8
% surviving at (age):							

10	[redacted]	99.7%	99.9%	100.0%	100.0%	100.0%	100.0%
20	[redacted]	90.3%	60.7%	76.1%	88.2%	97.0%	97.0%
30	[redacted]	69.9%	26.0%	34.6%	45.0%	7.3%**	14.5%
40	[redacted]	37.8%	13.6%	15.3%	12.3%	NA	0.6%
50	[redacted]	18.7%	7.3%	6.4%	2.8%	NA	NA

Abbreviations: GCS: glucocorticoids; NA: not available; NHM: natural history model

*% surviving based on last available data point at age 38. **% surviving based on last available data point at age 29.

8.1.1.2 Extrapolation of Loss of Ambulation, Non-Invasive Ventilation, and FVC<1L (MAIC)

A summary of assumptions regarding extrapolation of Loss of Ambulation, Non-invasive Ventilation, and FVC<1L for givinostat using the MAIC is described in Table 25. Due to the assumptions required in the MAICs, the rankings of AIC and BIC scores are the same for all outcomes – see Section 0 (Appendix) – and are therefore presented in the same summary table. No extrapolations for these endpoints have been done for the natural history, which were sourced from the original NHM.

Table 25: Summary of assumptions associated with extrapolation of Loss of Ambulation, Non-invasive Ventilation, and FVC<1L based on the MAIC

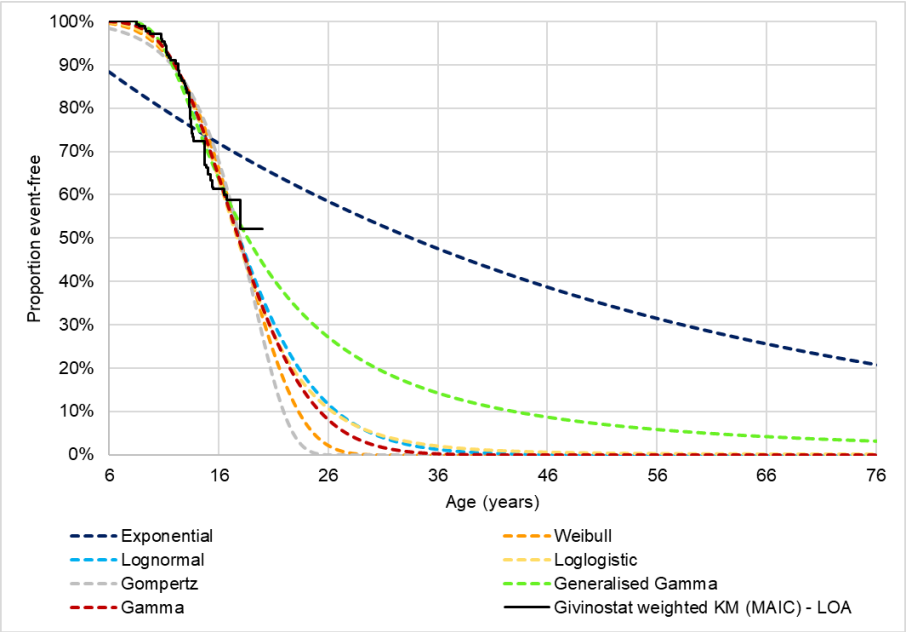
Method/approach	Description/assumption
Data input	EPIDYS, Study 51, and UK real-world data study (see MAIC described in section 7)
Model	Full parametrization
Assumption of proportional hazards between intervention and comparator	Yes
Function with best AIC fit	Givinostat: Generalised Gamma
Function with best BIC fit	Givinostat: Lognormal
Function with best visual fit	Givinostat: Lognormal
Function with best fit according to evaluation of smoothed hazard assumptions	Givinostat: Lognormal
Validation of selected extrapolated curves (external evidence)	NA
Function with the best fit according to external evidence	Givinostat: Lognormal
Selected parametric function in base case analysis	Givinostat: Lognormal
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	No (not applicable)
Assumptions of waning effect	For patients discontinuing givinostat, transition probabilities equal to the average of SoC and givinostat
Assumptions of cure point	No

Abbreviations: MAIC: Matching adjusted indirect comparison; NA: Not available; SoC: Standard of Care

Independent parametric curves were fit to the MAIC-weighted Kaplan-Meier data in accordance with the NICE DSU 14; the exponential, Weibull, Gompertz, log-normal, log-logistic, generalized gamma, and standard parametric curves were fit to these data (Latimer 2013). Figure 9, and Figure 11 present the extrapolated independent parametric curves fitted to the MAIC-weighted givinostat data for loss of ambulation, non-invasive

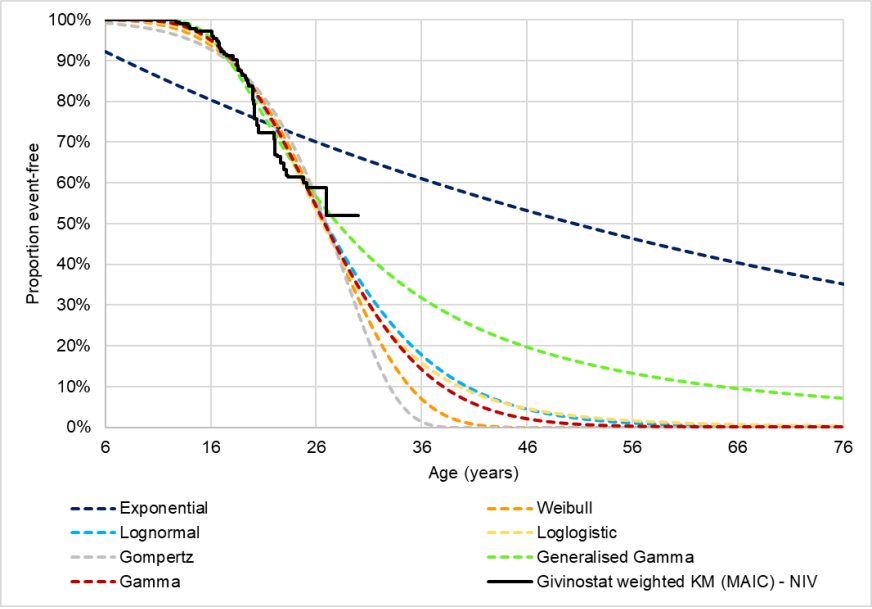
ventilation, and FVC<1L outcomes, respectively. The corresponding AIC and BIC values are presented in Table 72 (Appendix D). Table 73 in Appendix D presents the predicted median age at loss of ambulation, non-invasive ventilation, and FVC<1L across all parametric curves.

Figure 9: Independent standard parametric curves fit to the MAIC-weighted Kaplan-Meier data for age at loss of ambulation (givinostat)



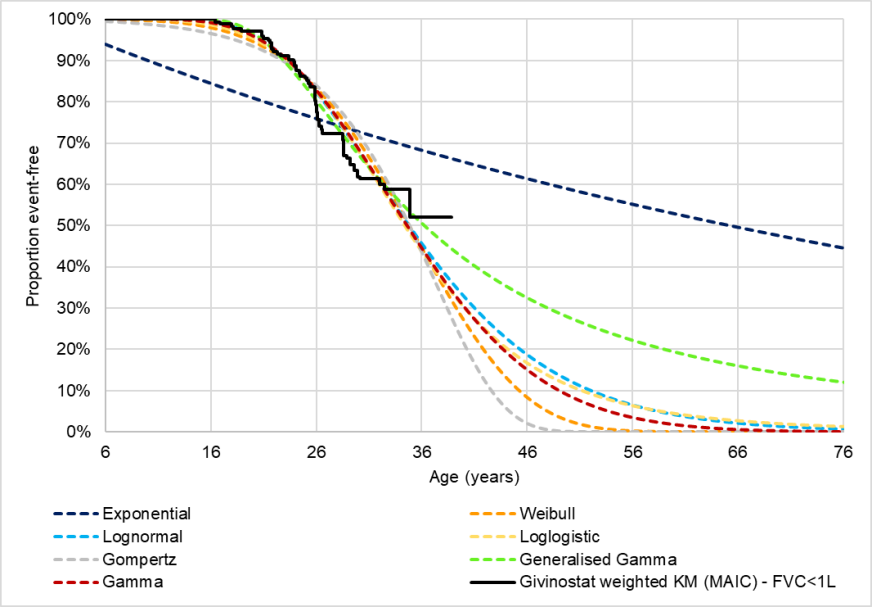
Abbreviations: KM: Kaplan-Meier; LOA: loss of ambulation; MAIC: matched adjusted indirect comparison.

Figure 10: Independent standard parametric curves fit to the MAIC-weighted Kaplan-Meier data for age at non-invasive ventilation (givinostat)



Abbreviations: KM: Kaplan-Meier; MAIC: matched adjusted indirect comparison; NIV: non-invasive ventilation.

Figure 11: Independent standard parametric curves fit to the MAIC-weighted Kaplan-Meier data for age at FVC<1L (givinostat)



Abbreviations: FVC: forced vital capacity; KM: Kaplan-Meier; MAIC: matched adjusted indirect comparison.

Summary of relative effect applied in the CEM

The above analyses result in a HR of 0.51 being applied for transitions from health states (1) to (2), (2) to (3), and (3) to (4), a HR of 0.39 being applied for transitions from health states (4) to (5), (4) to (6), and (5) to (7a), and a HR of 0.46 being applied for transitions from health states (6) to (7b), (7a) to (8a), and (7b) to (8b). Table 26 presents the HRs informing the individual health state transitions used in the CEM along with their confidence intervals. As the SOLVER function was used to derive hazard ratios that align the model with the lognormal distribution predictions for the three endpoints, the same approach was applied to derive confidence intervals by identifying hazard ratios that produce the lower and upper median values from the lognormal distribution. These HRs are applied to the transition probabilities estimated through the updated NHM to inform the efficacy for givinostat in the CEM. As givinostat is not anticipated to directly impact the probability of dying, HRs of one are applied to all transitions to death. Predicted median milestones are compared to those from the observed data and the fitted parametric curves in Table 27. The predicted event-free proportions for loss of ambulation, age at non-invasive ventilation, and age at FVC<30% by the CEM over the model time horizon are compared to the log-normal, generalized gamma, and gamma parametric curves fit to the MAIC-weighted givinostat data i.e., the best fitting parametric curves in Figure 47, Figure 48, and Figure 49 respectively. The predicted outcomes from the CEM are shown to align across the observed data and best fitting parametric curves, highlighting the validity of the CEM predictions.

Table 26: HRs applied to health state transitions in the CEM

Health state transitions	HR	Lower CI	Upper CI
To state 2 - Late ambulatory	0.51	****	****

To state 3 – Transfer	0.51	[redacted]	[redacted]
To state 4 - HTMF, no ventilation	0.51	[redacted]	[redacted]
To state 5 - No HTMF, no ventilation	0.39	[redacted]	[redacted]
To state 7a - No HTMF, night-time ventilation	0.39	[redacted]	[redacted]
To state 8a - Full time ventilation	0.46	[redacted]	[redacted]
To state 6 - HTMF, night-time ventilation	0.39	[redacted]	[redacted]
To state 7b - No HTMF, night-time ventilation	0.46	[redacted]	[redacted]
To state 8b - Full time ventilation	0.46	[redacted]	[redacted]
Mortality transitions	**HR**		
All state transitions above:	1.00		

Note: Lower and upper confidence intervals are derived from the lower bound of the medians for the log-normal distribution.

Abbreviations: CEM: cost-effectiveness model; HR: hazard ratio; HTMF: hand-to-mouth function.

Table 27: Median age at milestones

	Model predictions		MAIC Kaplan-Meier data		Parametric curves fit to MAIC-weighted givinostat data		
Median age at:	**SoC**	**Givinostat**	**SoC**	**Givinostat**	**Log-normal**	**Generalised gamma**	**Gamma**
Unable to stand from supine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Loss of ambulation	12.08	[redacted]	[redacted]	Weighted = [redacted] Unadjusted = [redacted]	[redacted]	[redacted]	[redacted]
Loss of HTMF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Starting ventilation	[redacted]	[redacted]	[redacted]	Weighted = [redacted] Unadjusted = [redacted]	[redacted]	[redacted]	[redacted]
Starting full-time ventilation	[redacted]	[redacted]	[redacted]	Weighted = '' Unadjusted = [redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CEM: cost-effectiveness model; HR: hazard ratio; HTMF: hand-to-mouth function; MAIC: matched adjusted indirect comparison; NA: not available; NE: not evaluable.

8.1.2 Calculation of transition probabilities

A summary of elicitation of transition probabilities is presented in Table 28. Refer to Appendix M for more details on derivation of transition probabilities.

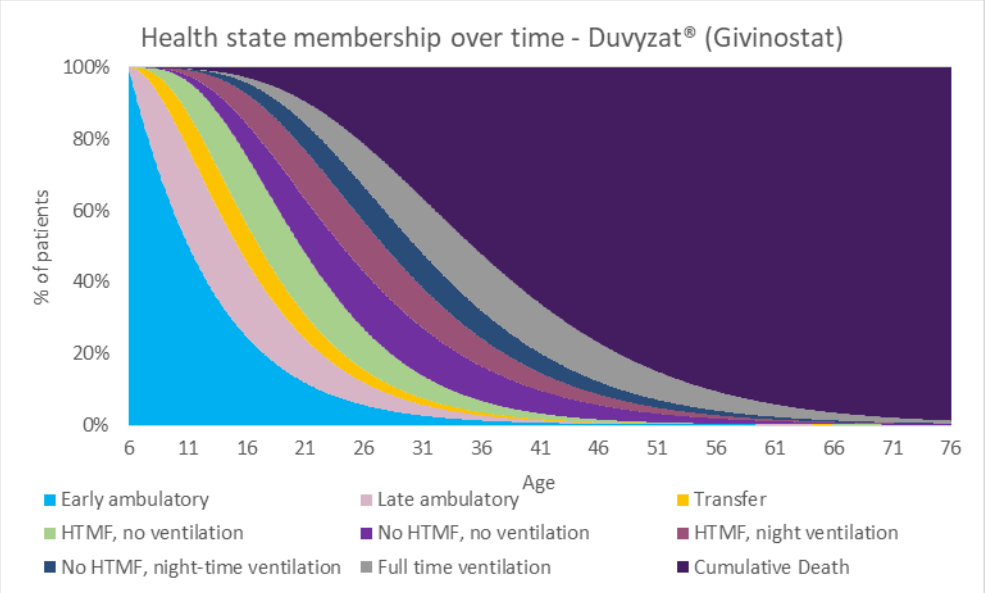
Table 28: Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
Health state 1–8	Health state 2–8	NHM: Using transition intensities estimated using the C-Path-D-RSC Dataset. See Figure 3.	Broomfield et al. (2024) and MAIC (see section 7)
Health state 1–8	Death (9)	NHM: Using transition intensities estimated using the C-Path-D-RSC Dataset. See Figure 3.	Broomfield et al. (2024)

Abbreviations: CEM: Cost-effectiveness model; HR: Hazard ratio; MAIC: Matching-adjusted indirect comparison; NHM: Natural history model

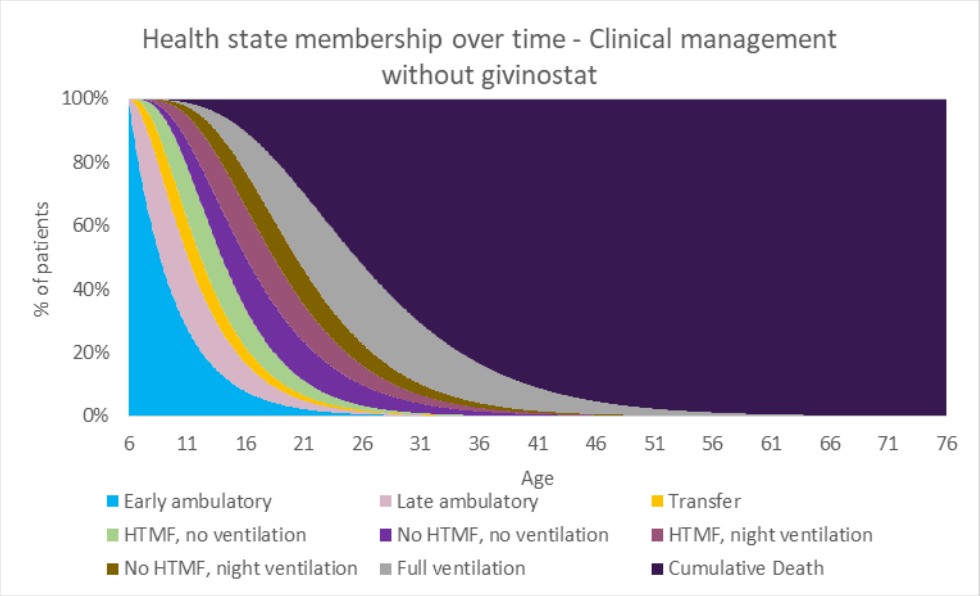
Modelled health state membership over time for givinostat and SoC are described in Figure 12 and Figure 13, respectively.

Figure 12: Health state membership over time - Givinostat



Abbreviations: HTMF: hand-to-mouth function

Figure 13: Health state membership over time – SoC



Abbreviations: HTMF: hand-to-mouth function

8.2 Presentation of efficacy data from [additional documentation]

Not applicable.

8.3 Modelling effects of subsequent treatments

Not applicable, no subsequent treatments are modelled.

8.4 Other assumptions regarding efficacy in the model

For patients who discontinue treatment with givinostat, the CEM assumes that health state transitions are an average between the health state transition on givinostat and in the SoC arm. The evidence supporting these transitions is demonstrated by the correlations between improved earlier outcomes and improved later outcomes widely documented in the DMD literature, see section 0.

8.5 Overview of modelled average treatment length and time in model health state

As indicated by Table 29, the predicted median age at loss of ambulation and death are in line with UK real-world data. Additional details on validations are presented in Appendix C. The model's predictions for the median age at the different disease milestones were also validated by an independent Danish paediatric clinician

(Italfarmaco 2024c), demonstrating that the model well captures the disease trajectory of Danish DMD patients treated with GCs. Modelled median age at LoA was largely in line with UK real-world data (12.08 vs. 12.1 years in the SoC arm). Modelled age at death was [redacted] than the UK real-world data [redacted] vs. 28 years). The Danish RWD showed a mean age at death of 26.8 years (IQR:19-34) (Rudolfsen et al. 2024).

Table 29: Estimates in the model

	Modelled median age at death ("Base-case results")	Observed median age at death from relevant study	Modelled median age at LoA ("Base-case results")	Observed median age at LoA from relevant study
Givinostat	[redacted] years	[redacted]	[redacted] years	[redacted]
SoC	[redacted] years	28.0 years (UK real-world data)	12.08 years	12.1 years (UK real-world data)

Abbreviations: LoA: Loss of ambulation; SoC: Standard of care; UK: United Kingdom.
*In latest analysis on data from OLE study the median age at loss of ambulation was 18.1 [redacted] for patients treated with givinostat at study entry (Italfarmaco 2025a).

Modelled average treatment length and time in health states are described in Table 30. Average treatment length with givinostat was [redacted] years. However, patients were allowed to continue with add-on GCs after discontinuation of givinostat. Average treatment length with add-on GCs in the givinostat arm was [redacted] years.

Table 30: Overview of modelled average treatment length and time (years) in model health state, undiscounted and not adjusted for half cycle correction

Treatment	Treatment length	HS 1	HS 2	HS 3	HS 4	HS 5	HS 6	HS 7	HS 8
Givinostat	[redacted] add-on GCs)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HS: Health state; SoC: Standard of care

9. Safety

9.1 Safety data from the clinical documentation

9.1.1 EPIDYS

In EPIDYS, the Safety population was used for safety evaluations and comprised all randomly assigned boys who received at least one dose of study drug (i.e. the Overall ITT population), with treatment group assignment defined by the treatment received (Mercuri et al. 2024b, Mercuri et al. 2024c). A summary of givinostat safety is provided in Table 31. For a more detailed description of treatment compliance and exposure, dose modifications and treatment discontinuation, and AEs, including treatment-related AEs, see Appendix E.

A summary of AEs from EPIDYS is provided in Table 31. Most AEs were mild to moderate, and no life-threatening AEs were reported. The most frequently reported treatment-related AEs were blood triglycerides increased/hypertriglyceridaemia, diarrhoea, thrombocytopenia/platelet count decreased, blood thyroid stimulating hormone increased, abdominal pain and troponin increased (Italfarmaco 2024s).

Table 31: Overview of safety events in EPIDYS (Mean treatment duration 493 days)

	EPIDYS		
	Givinostat (n=118)	**Control (n=61)**	**Difference, % (95 % CI)**
Number of adverse events, n	1046	398	-
Number and proportion of patients with ≥1 adverse events, n (%)	112 (94.9)	57 (93.4)	1.47% (-5.90, 8.84)
Number of serious adverse events*, n	9	2	-
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	8 (6.8)	2 (3.3)	3.50% (-2.87, 9.87)
Number of CTCAE grade ≥ 3 events, n	N/A	N/A	N/A
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	5 (4.2)	1 (1.6)	2.60 (-2.24, 7.43)
Number of adverse reactions, n	N/A	N/A	N/A
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	81 (26.3)	17 (27.9)	40.78% (26.75, 54.80)
Number and proportion of patients who had a dose reduction, n (%)	42 (35.6)	1 (1.6)	33.95% (24.75, 43.16)
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	7 (5.9)	2 (3.3)	2.65% (-3.52, 8.83)
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	Temporary 16 (14.2) Permanent 4 (3.4)	Temporary 4 (6.6) Permanent 0 (0)	Temporary 7.00% (-1.76, 15.76) Permanent 3.39% (-0.70, 7.48)

No boys died during the EPIDYS study (Mercuri et al. 2024b, Mercuri et al. 2024c). Overall, eight (7%) boys in the givinostat group and two (3%) boys in the placebo group reported at least one serious adverse event (SAE) (Table 32) (Mercuri et al. 2024b, Mercuri et al. 2024c). No SAEs were considered related to the study drug or led to withdrawal. SAEs in the givinostat group included gastroenteritis, gastroenteritis viral, influenza, abdominal pain, vomiting, chest pain, spinal fracture, dizziness, and rash - all reported by one (1%) boy each (Mercuri et al. 2024b, Mercuri et al. 2024c). No SAE had a frequency ≥ 5% (Table 32). However, these are recognised adverse events of givinostat and can generally be managed by dose reduction or interruption. Indeed, adverse event

monitoring in the current study (with subsequent dose adjustment) was successful—95% of participants completed the study, and treatment compliance was high, 98%.

Table 32: Serious adverse events in EPIDYS with a frequency ≥ 5% (18 months)

Adverse events	Givinostat (N=118)		Placebo (N=61)	
	Number of patients with adverse events, n (%)	Number of adverse events	Number of patients with adverse events, n (%)	Number of adverse events
N/A (as no SAE in EPIDYS had a frequency that was ≥ 5%)				

Abbreviations: N: number of boys in the analysis set
References: EPIDYS Clinical study report (2022) (Italfarmaco 2022a)

9.1.2 OLE

At December 2023 DCO, the mean actual duration of givinostat treatment was [redacted] days (standard deviation [SD] [redacted]days* range [redacted] to [redacted]days; mean actual duration [redacted]days in the givinostat group[redacted]days in the delayed givinostat group, and [redacted]days in the naïve givinostat group) (Italfarmaco 2024s). The maximum givinostat exposure in the OLE was 6.1 years, but 16 patients were previously treated for up to 4 years in Study 43, giving a maximum total exposure time of 10.1 years (Italfarmaco 2022a, Italfarmaco 2024s). Mean administration compliance was[redacted]similar across all the givinostat treatment groups (Italfarmaco 2024s).

No new safety signals have been identified from the ongoing OLE study. Results from the December 2023 DCO confirm that givinostat has a predictable and acceptable safety and tolerability profile consistent with EPIDYS and other studies of givinostat (Italfarmaco 2024s).

Two boys/young men died during the OLE study, not related to givinostat treatment; one due to a road traffic accident and one due to thoracic haemorrhage, (Italfarmaco 2024s).

An overview of safety events during the OLE study is available in Appendix 0, Table 81.

9.1.3 Adverse events included in the health economic model

All treatment-related adverse events observed in at least 5% of patients in the EPIDYS trial were included in the health economic model (Table 33).

Table 33: Adverse events used in the health economic model

Adverse events	Intervention	Comparator		
	Frequency used in economic model for intervention	Frequency used in economic model for comparator	Source	Justification
Adverse event, n (%)				
Decreased platelet count	20 (16.9%)	0 (0%)	EPIDYS	Treatment-related TEAEs reported in ≥5% of the subjects
Thrombocytopenia	19 (16.1%)	0 (0%)		

Adverse events	Intervention	Comparator	
Increased blood triglyceride concentration	14 (11.9%)	3 (4.9%)	(standard practice)
Hyperglyceridaemia	13 (11.0%)	1 (1.6%)	
Diarrhoea	25 (21.2%)	2 (3.3%)	
Abdominal pain	16 (13.6%)	2 (3.3%)	
Upper abdominal pain	9 (7.6%)	1 (1.6%)	
Vomiting	7 (5.9%)	0 (0%)	

9.2 Safety data from external literature applied in the health economic model

Not applicable.

10. Documentation of health-related quality of life (HRQoL)

Data on HRQoL used in the CEM are sourced from literature. The EQ-5D instrument was not included in the trial program. Therefore, HRQoL results from the clinical trials are shown in Appendix F.

Table 34: Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
See Appendix F.		

10.1 Presentation of the health-related quality of life measured by PODCI

10.1.1 Study design and measuring instrument

See Appendix F.

10.1.2 Data collection

See Appendix F.

10.1.3 HRQoL results

See Appendix F.

10.2 Health state utility values (HSUVs) used in the health economic model

The studies forming the basis for clinical effectiveness have not been applied for health state utility values. Hence, this section is not applicable.

10.2.1 HSUV calculation

Not applicable.

10.2.1.1 Mapping

Not applicable.

10.2.2 Disutility calculation

Not applicable.

10.2.3 HSUV results

Table 35: Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Not applicable				

10.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

The CEM leveraged patient utilities derived from literature and in the base case health state patient utilities from Audhya et al. (2023b) are applied. The health states utilities reported by Audhya et al. (2023b) are used as its measurements align with the health states specified in the CEM and the study offer significant advancements by estimating EQ-5D utility values for an extensive range of DMD clinical and functional health states directly from patients. Furthermore, the study not only reflects the most current data but also improves accuracy and relevance by shifting the data collection from caregiver to patient-reported outcomes.

Based on published literature which has shown that informal caregiving in DMD is frequently associated with reduced HRQoL, poor sleep quality, impaired family function, depression, pain, stress, sexual dysfunction, and/or lower self-esteem, as well as considerable impact on work life and productivity (Landfeldt 2018), caregiver utilities have been included as a scenario analysis and are derived from Landfeldt et al. (2017a); utilities for the non-ventilation associated health states (1-6) are taken from “Model II: (ambulatory status)” from table 1, whereas utilities ventilation-associated health states (7-8) are taken from “Model III: (ventilations status)” from table 1. Landfeldt et al.

(2017a) is a cost-effectiveness study, evaluating a hypothetical DMD intervention versus standard care in the UK (see section 10.4 for details). The substantial impact on HRQoL for caregivers and family members have also emphasized by a Nordic (Norwegian) neuromuscular expert (Italfarmaco 2024f).

10.3.1 Study design

The study by Audhya et al. (2023b) aimed to estimate EQ-5D-5L and HUI utility values based on patient-reported health status for a range of health states reflecting different clinical and functional conditions in DMD.

Individuals with DMD in the U.S., aged 12–40 years, completed the EQ-5D-5L and Health Utilities Index (HUI) preference-based instruments. Using a clinical questionnaire, participants self-classified into functional health states based on lower and upper limb function, respiratory support use, and presence of cardiomyopathy. Mean utility scores and EQ-5D-5L visual analogue scale (VAS) scores, along with standard deviations (SD), were estimated for each health state. Additionally, median and interquartile range (IQR) attribute levels were calculated to identify the most severely affected health domains in DMD. The study used a US-value set to transform the EQ-5D-5L health states to utility weights (Audhya et al. 2023b) (Table 36).

10.3.2 Data collection

A web-based survey was used to collect self-reported data from study participants. The survey included a clinical questionnaire to assess the extent and severity of DMD symptoms, a series of demographic questions to characterize the study population, and validated preference-based measures of HRQoL, including the Health Utilities Index (HUI) and the EQ-5D-5L (Audhya et al. 2023b).

The clinical questionnaire aimed to evaluate the patient's functional health state through self-assessment of primary and secondary manifestations relevant to DMD's natural history. These manifestations encompassed lower and upper limb function, use of respiratory support due to respiratory insufficiency, and presence of symptomatic cardiomyopathy—both key indicators of disease severity. These aspects were identified as significant from both patient and caregiver perspectives (Audhya et al. 2023b).

Due to the relatively small sample size for certain health states and to facilitate comparisons with existing utility values, health states were also categorized based on lower and upper limb function alone. Lower limb function was used to classify patients as early ambulatory, late ambulatory (transitional), or non-ambulatory. Among non-ambulatory individuals, those with little to no upper limb involvement were classified as early non-ambulatory, while those with moderate to severe upper limb impairment (loss of function) were classified as late non-ambulatory (Audhya et al. 2023b).

10.3.3 HRQoL Results

Audhya et al. (2023b) did not study any interventions and did only collect data at a single time point. Hence, all results are results are reported in section 10.3.4.

10.3.4 HSUV and disutility results

The study found significant variability in utility scores across different health states and measurement instruments. Ambulatory patients without cardiomyopathy reported higher utility values, while non-ambulatory patients with impaired upper limb function and need for respiratory support showed markedly lower utility.

The health state definitions varied between the study by Audhya et al. (2023b) and the CEM. To ensure that the health states in Audhya et al. (2023b)were correctly mapped to the health states in CEM, several clinical experts were assigned a mapping exercise. However, the clinical experts suggested that some of the health states in Audhya et al. (2023b) were overlapping with more than one health state defined in PH (Broomfield et al. 2024). As a result, a weighted average was derived from the health state utility values (HSUVs) stated in Audhya et al. (2023b), when two or more health states from Audhya et al. (2023b) corresponded to a single health state in the model, following which the HSUVs were assigned to each of the health states in the current CEM.

Due to a lack of observations (n=1) in certain health states in Audhya et al. (2023b) and to ensure utilities included in the model had face validity, a weighted average of multiple health states that corresponded to a single health state in NHM (based on expert opinion, N=1), was considered to calculate the utility of each health state. Additionally, due to a lack of data on the disutility of nighttime ventilation, the utility decrement was arbitrarily assumed to be 5% for patients with night-time ventilation than those without night-time ventilation (Table 36).

Disutilities for adverse events were included in the model, sourced from the NICE Vamorolone assessment (table 57, original sources: Sullivan et al. (2011) and Hagiwara et al. (2018)). Duration of adverse events were assumed to be 3.5 days for diarrhoea, abdominal pain, upper abdominal pain, and 1.8 days for vomiting, based on the NICE Vamorolone assessment.

Table 36: Overview of health state utility values and disutilities

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				**Corresponding health states mapped by Audhya et al. (2023b)**
1 - Early ambulatory	0.790 (NA)	EQ-5D-5L	US	**Early ambulatory:** *Preserved upper limb, no daytime ventilation, without symptomatic CM *Mildly impaired upper limb, no daytime ventilation, without symptomatic CM
2 - Late ambulatory	0.640 (NA)	EQ-5D-5L	US	**Late ambulatory:** *Transitional, preserved upper limb, no daytime ventilation, without symptomatic CM *Transitional, mildly impaired upper limb, no daytime ventilation, without symptomatic CM
3 - Transfer	0.640 (NA)	EQ-5D-5L	US	**Late ambulatory:**

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
				*Transitional, preserved upper limb, no daytime ventilation, without symptomatic CM *Transitional, mildly impaired upper limb, no daytime ventilation, without symptomatic CM
4 - HTMF, no ventilation	0.314 (NA)	EQ-5D-5L	US	**Weighted average across health states in early non-ambulatory (0.3138):** *Preserved upper limb, no daytime ventilation, without symptomatic CM *Mildly impaired upper limb, no daytime ventilation, without symptomatic CM *Mildly impaired upper limb, no daytime ventilation, with symptomatic CM
5 - No HTMF, no ventilation	0.231 (NA)	EQ-5D-5L	US	**Weighted average across health states in late non-ambulatory (0.2307):** *Moderately impaired upper limb, no daytime ventilation, without symptomatic CM *Moderately impaired upper limb, nighttime and daytime ventilation, without symptomatic CM
6 - HTMF, night-time ventilation	0.299 (NA)	EQ-5D-5L	US	**Weighted average across health states in early non-ambulatory (0.3138):** *Preserved upper limb, no daytime ventilation, without symptomatic CM *Mildly impaired upper limb, no daytime ventilation, without symptomatic CM *Mildly impaired upper limb, no daytime ventilation, with symptomatic CM *-5% utility decrement due to nighttime ventilation (0.2987)
7 - No HTMF, night-time ventilation	0.219 (NA)	EQ-5D-5L	US	**Weighted average across health states in late non-ambulatory (0.2307):** *****Moderately impaired upper limb, no daytime ventilation, without symptomatic CM *****Moderately impaired upper limb, nighttime and daytime ventilation, without symptomatic CM *-5% utility decrement due to nighttime ventilation (0.2987)
8 - Full time ventilation	0.211 (NA)	EQ-5D-5L	US	**Weighted average across health states in late non-ambulatory (0.211):** *Moderately impaired upper limb, no daytime ventilation, with symptomatic CM *Loss of upper limb function, nighttime and daytime ventilation, without symptomatic CM *Loss of upper limb function, no daytime ventilation, without symptomatic CM *Loss of upper limb function, nighttime and daytime ventilation, without symptomatic CM
Disutilities				**Source**

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Decrease platelet count	0			Assumption
Thrombocytopenia	0			Assumption
Increased blood triglyceride concentration	0			Assumption
Hyperglyceridaemia	0	EQ-5D	UK	Assumption
Diarrhoea	0.0470	EQ-5D	UK	Vamorolone NICE committee papers (see table 57) original source: Sullivan et al. (2011)
Abdominal pain	0.0470	EQ-5D	UK	Assumed same as diarrhoea
Upper abdominal pain	0.0470	EQ-5D	UK	Assumed same as diarrhoea
Vomiting	0.0950	EQ-5D	UK	Vamorolone NICE committee papers (see table 57) original source: Hagiwara et al. (2018)

Abbreviations: CI: Confidence interval; CM: Cardiomyopathy; NA: Not available

In Project Hercules, health state utilities were leveraged from the utilities derived by Landfeldt et al. (2017a). The study provided utility values for four health states: early ambulatory, late ambulatory, early non-ambulatory, and late non-ambulatory (see Appendix F2 for details). As the economic model includes eight health states, some of the utility values were used for multiple health states in the interim. The model applied early and late ambulatory values to health states one and two, respectively. The early non-ambulatory utility value was applied to the intermediate health states 4 to 6. For health states 7 and 8, the late non-ambulatory value was applied. Given the availability of HRQoL data derived from Audhya et al. (2023b), the experts suggested to use the utilities reported in that study for the CEM.

Table 37 presents the health state utility weights from Landfeldt et al. (2017a) which were included in a sensitivity analysis, in addition to the other weights identified in the SLR (Audhya et al. 2023b).

Table 37: Overview of literature-based health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
1 - Early ambulatory				
Audhya et al. (2023b)	0.790 (NA)	EQ-5D-5L	US	Used in base case
Landfeldt et al. (2017a)	0.699 (0.628, 0.770)	HUI	UK	Used in sensitivity analysis
2 – Late ambulatory				
Audhya et al. (2023b)	0.640 (NA)	EQ-5D-5L	US	Used in base case

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Landfeldt et al. (2017a)	0.607 (0.550, 0.664)	HUI	UK	Used in sensitivity analysis
3 - Transfer				
Audhya et al. (2023b)	0.640 (NR)	EQ-5D-5L	US	Used in base case
Landfeldt et al. (2017a)	0.607 (0.550, 0.664)	HUI	UK	Used in sensitivity analysis
4 - HTMF, no ventilation				
Audhya et al. (2023b)	0.231 (NR)	EQ-5D-5L	US	Used in base case
Landfeldt et al. (2017a)	0.224 (0.197, 0.251)	HUI	UK	Used in sensitivity analysis
5 - No HTMF, no ventilation				
Audhya et al. (2023b)	0.231 (NR)	EQ-5D-5L	US	Used in base case
Landfeldt et al. (2017a)	0.224 (0.197, 0.251)	HUI	UK	Used in sensitivity analysis
6 - HTMF, night-time ventilation				
Audhya et al. (2023b)	0.299 (NR)	EQ-5D-5L	US	Used in base case
Landfeldt et al. (2017a)	0.224 (0.197, 0.251)	HUI	UK	Used in sensitivity analysis
7 - No HTMF, night-time ventilation				
Audhya et al. (2023b)	0.219 (NR)	EQ-5D-5L	US	Used in base case
Landfeldt et al. (2017a)	0.146 (0.126, 0.166)	HUI	UK	Used in sensitivity analysis
8 - Full time ventilation				
Audhya et al. (2023b)	0.211 (NA)	EQ-5D-5L	US	Used in base case
Landfeldt et al. (2017a)	0.146 (0.126, 0.166)	HUI	UK	Used in sensitivity analysis

Abbreviations: HTMF: Hand to mouth function, NA: Not available

10.4 Other sources of HRQoL in DMD

For information on sources for utility please see Appendix F1

11. Resource use and associated costs

The model includes health state costs and medicine acquisition costs. In the health state cost, direct medical costs are provided as a bulk cost, hence micro costing is not applied.

11.1 Medicines - intervention and comparator

Costing by prescriptions per cycle reflects the economic cost of being prescribed givinostat i.e. the one-off cost of receiving one givinostat bottle. The cost of givinostat is based on the calculation of the number of prescriptions needed at each cycle, based on dosage by weight band (15–20 kg, 20–40 kg, 40–60 kg, 60+kg) aligned with the SmPC (see Table 40 below). Costing by prescription instead includes drug leftovers in the total cost of dispensing.

The model calculates the total number of prescriptions needed to treat one patient, cumulatively at each cycle, dividing the total number of days in the model by the average duration of one bottle for each dosage, and the incident number of prescriptions, i.e. the difference between the number of bottles needed at cycle t minus the number of bottles at cycle t-1. Compliance is accounted for in the model ([total number of expected doses - the total number of missed doses]/ total number of expected doses), with the value of 98.3% for givinostat and 98.12% for GCs taken from the EPIDYS trial. RDI is not included in the base case (84.6% and 90.21% for givinostat and GCs, respectively, in the EPIDYS trial), but is included in a sensitivity analysis. The model assumes a 0.34% rate of discontinuation per month for givinostat, and 0.19% for GCs, based on EPIDYS. In EPIDYS, 7 patients discontinued givinostat and 2 patients discontinued GCs over 18 months follow-up.

Dose, RDI frequency and vial sharing assumption are presented in Table 38. The drug cost as cost per pack, strength, and pack size, and dose are provided in Table 39.

Table 38: Medicines used in the model

Medicine	Dose	RDI	Frequency	Vial sharing
Givinostat	The expected dosing of givinostat is in accordance with the recommended dosage presented in the SmPC (Table 5). In case of adverse reactions, the dosage will be modified according to recommendations in the SmPC (Table 6)	100%	Twice daily	No
Prednisone	0.75 mg/kg	100%	Once daily	NA
Deflazacort	0.90 mg/kg	100%	Once daily	NA

Abbreviations: NA: Not applicable, RDI: Relative dose intensity

Table 39 Medicine acquisition costs

	Strength	Pack size	AIP excluding VAT, pr. Pack*
Givinostat (Duvyzat)	8.86 mg/mL	One bottle 140 mL	122 995
Prednisolone	5 mg	100	56.38
Deflazacort	6 mg	60	845.00

Abbreviations: AIP: Pharmacy purchase price, DKK: Danish krone, VAT: value added tax

In addition to costing by prescriptions per cycle (4 dose bands), two additional costing approaches for givinostat are available in the health economic model. The first one is costing by prescriptions per cycle using 5 dose bands, which does not align with the SmPC where instead 4 dose bands are considered. The second option is costing by cycle consumption. Costing by cycle consumption is the cost per cycle, i.e. the total amount of givinostat required over the cycle duration, i.e. 30.44 days per cycle. This calculation assumes that givinostat is dispensed by milligram [or millilitre] and does not consider the cost of drug discarded when a patient stops treatment (due to treatment discontinuation, death or other reason). Costing by strict cycle consumption implies that, for every patient, the amount left in a bottle can be shared with other patients.

Additionally, the model allows to also take into account the variability on dosing in each weight band, adding the proportion of people that receive the initial full dose (A) or reduced doses (band B and band C) taken from the EPIDYS trial, see Table 41 below. This method does not consider the mean weight of patients in each health state but considers the distribution of mean weight, meaning that one can assume that in each cycle certain % of patients will be in each weight band. Then for each dose (A, B and C) it estimates the new number of prescriptions (bottles) you would need per each weight category and cycle.

Table 40. Givinostat Dosage (SmPC).

Dose		15-20Kg	20-40 Kg	40-60 kg	60+ kg
Dose A	Oral suspension (mL)	2.50	3.50	5.00	6.00
	Dose A per day (mg)	44.40	62.00	88.60	106.40
Dose B	Oral suspension (mL)	2.00	2.50	3.50	4.50
	Dose B per day (mg)	35.40	44.40	62.00	79.80
Dose C	Oral suspension (mL)	1.50	2.00	3.00	4.00
	Dose C per day (mg)	26.60	35.40	53.20	70.80

Abbreviations: mg, milligrams; ml, millilitres; kg, kilograms; SmPC, Summary of Product Characteristics.

Table 41. Proportion of Patients per dose and per Weight Category according to EPIDYS study

	15-20Kg	20-40 Kg	40-60 kg	60+ kg
% dose A	[redacted]	[redacted]	[redacted]	[redacted]
% dose B	[redacted]	[redacted]	[redacted]	[redacted]
% dose C	[redacted]	[redacted]	[redacted]	[redacted]
TOTAL	100.00%	100.00%	100.00%	100.00%

Abbreviations: kg, kilograms.

Source: Mercuri et al. (2024b)

11.2 Medicines– co-administration

No co-administered drugs. Glucocorticoids are given concomitant to givinostat and are described in the intervention section (section 11.1)

11.3 Administration costs

No administration costs are included in the model since all included treatments are orally administered.

Table 42: Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
Not applicable				

11.4 Disease management costs

Health state costs are the ongoing costs of disease management, which increase as DMD progresses. Activities differ depending on the disease stage, and as the disease progresses, the unit costs of some activities will also increase to reflect the increased resource use and time required to undertake monitoring or a healthcare intervention (Landfeldt et al. 2014).

Due to lack of data on resources and disease management costs of DMD patients over the course of disease progression in Denmark, UK cost data from the Landfeldt et al. (2017a) study was used in the model. Landfeldt et al. collected costs of care of DMD patients in Germany, Italy, UK and United States, mapped to health states. These included direct medical costs, such as hospital admissions, consultations with physicians and healthcare professionals, medical test and evaluations, medications, and emergency

and respite care. Non-medical cost was also assessed and relating to cost on non-medical aids and investments. The study further included informal care costs such as paid and unpaid informal care, and indirect costs encompassing productivity loss for both the patient and primary caregiver (Landfeldt et al. 2017a). The direct medical cost was calculated using resource use for DMD patients over their disease progression (Landfeldt et al. 2017a) .

Landfeldt et al. identified male patients with DMD diagnosis aged 5 years or older from national DMD registries. Cost data were collected from questionnaires completed by the patients and one of their caregivers. Generalised linear models were fitted to the cost data assuming a gamma distribution with a log link, with ambulatory status as the main explanatory variable. Landfeldt et al. (2017a) provides healthcare costs based on resource use reflecting disease progression of patients with DMD. In the model only direct medical costs have been included. Costs have been inflated from 2015 to 2024 using Bank of England inflation calculator and converted from British pound to DKK using the average exchange rate of 2015 from the central bank of Denmark (10.28 DKK/GBP) and are provided in Table 43.

Table 43: Health State costs

Ambulatory status	Direct medical costs (DKK)	Resource use included in health state costs
Early ambulatory	130 744	Hospital admissions, emergency care, respite care, visits to physicians, visits to other health care practitioners, test and assessments, medications, medical aids, devices, community services.
Late ambulatory	137 115	
Transfer	137 115	
HTMF, no ventilation	202 058	
No HTMF, no ventilation	202 058	
HTMF, night-time ventilation	202 058	
No HTMF, night-time ventilation	338 071	
Full time ventilation	338 071	

Abbreviations: HTMF: Hand-to-Mouth Function

By using only direct heath states cost, the total economic burden of DMD is likely highly underestimated given the substantial burden faced by patients and carers. Many informal caregivers to patients with DMD terminate their employment or reduce their working hours to find the time needed to care for their children, and those who do continue to work have markedly impaired productivity with high levels of absenteeism (Landfeldt et al. 2016b). In a retrospective observational study in the Nordics (Sweden), the main driver of the total cost per patient was indirect costs, with the majority related to the cost of personal assistance and sick leave or activity compensation (Ekström et al. 2024). Hence, the main economic burden of DMD stems not from the direct medical cost, and by only modelling these the total burden is significantly underestimated. This was further confirmed by a Danish clinical expert who stated that the main resource use is personal assistance, e.g., assistance in school and for after school activities. Furthermore, and notably, once ventilation is used, assistance whether by a family members or respite care is needed 24 hours per day (Italfarmaco 2024c).

Moreover, a recent study highlighted the significant burden of DMD on caregivers and family members in the Danish setting, including increased healthcare utilization and financial strain for parents, as well as educational challenges and higher incidence of long-term sick leave for siblings (Rudolfsen et al. 2024). The study estimated that excess

costs associated with DMD (primary care, outpatient care, inpatient care, respiratory care, prescription medicines) for patients living to age of 18 years was EUR 452 100, and EUR 1 922 000 for patients living to the age of 30 years.

Since the unit costs for disease management are not based on DRG tariffs, Table 44 is not applicable.

Table 44: Disease management costs used in the model

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Not applicable				

11.5 Costs associated with management of adverse events

All treatment-related TEAEs occurring in ≥5% boys in either treatment arm observed in the overall population from EPIDYS have been included in the model. The AEs are assumed to be managed through dose reduction or handled during the monitoring of the disease. Hence, no cost is associated with occurrence of them.

Table 45: Cost associated with management of adverse events

	DRG code	Unit cost/DRG tariff
Not applicable		

11.6 Subsequent treatment costs

No subsequent treatments are included in the model since no other treatments for DMD are available.

Table 46: Medicines of subsequent treatments

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Not applicable				

11.7 Patient costs

Since the health state costs are aggregated, there is no explicit information available on specific resource consumption frequency. As a result, it has not been possible to include patient and caregiver time, as well as transportation costs, for the resources underpinning the health state costs. This makes the health state costs conservative in magnitude. For instance, caregivers must dedicate significant time to caring for a child with DMD. Notably, when full-time ventilation becomes necessary, the child requires constant supervision 24 hours a day (Italfarmaco 2024f, Aartsma-Rus et al. 2019).

Consequently, the ICER estimated in the health economic model should be considered very conservative in this regard.

Table 47: Patient costs used in the model

Activity	Time spent [minutes, hours, days]
Not applicable	

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

Once children lose ambulation, care is taken to closely monitor their spines and heart. The spine develops scoliosis i.e. curvature of the spine, which needs its own management and may require scoliosis surgery. As scoliosis progresses, it may have a significant impact on the respiratory system and affect positioning and comfort in a wheelchair (Cheuk et al. 2015). As a result, most patients with scoliosis undergo spinal fusion surgery (Cheuk et al. 2015). The impact of scoliosis on disease progression or mortality is assumed to be reflected in the transition probabilities from the updated NHM. Scoliosis is explicitly included in the model as cost of spinal surgery and the as utility decrement.

However, it is anticipated that treatment with givinostat will reduce the number of patients who require spinal fusion surgery beyond the impact reflected by the health state costs and utilities. Delaying the LoA, as observed in patients treated with givinostat, may avoid the period of growth in adolescents, during which the progression of scoliosis is fastest (Archer et al. 2016). Therefore, the need for surgery in future health states may be reduced.

The Danish burden of illness study by Rudolfsen et al. showed 54% of patients had a diagnosis of scoliosis (Rudolfsen et al. 2024). The same paper showed that 38% of patients had spine surgery (procedure code KNAG). This is in line with Pietrusz et al. (2023) which reported findings from a multicentre retrospective case note review, conducted between three UK hospitals (London, Newcastle, and Oxford). Note: these patients correspond to the dataset informing the unpublished UK real-world data used in the ITCs (Section 6.1.1.3) and the updated NHM (Section 7). The data indicate 51.4% (18/35) and 30.2% (19/63) of patients required scoliosis surgery across GC stopped and GC continued treatment arms, respectively, with an average surgery rate of 37.8% (18+19)/(35+63). The CEM assumes that 38% of patients in the SoC arm receive scoliosis surgery. Clinical expert (Italfarmaco 2024e) estimates that 30-35% of patient between 14-16 years of age undergo scoliosis surgery.

No cases of scoliosis surgery are observed in patients treated with givinostat in EPIDYS or the OLE study. As reported in McDonald et al. (2018), scoliosis surgery is assumed on average four years following loss of ambulation. As a conservative approach, the CEM assumes that the LoA HR for givinostat arm vs. SoC i.e. 0.51 is applied to the scoliosis surgery rate with SoC. This results in 14.8% of patients receiving scoliosis surgery in the

givinostat arm, which is a conservative estimate as most of the patients will be fully grown before losing ambulation due the delay in loss of ambulation.

In the CEM, spinal fusion surgery is assumed on average four years following loss of ambulation and patients are eligible for spinal surgery in the CEM from 15–25 years - aligned with data from McDonald et al. (2018) and assumptions in the NICE appraisal of Vamorolone for treating DMD (GID-TA11135) (NICE 2023b). Table 48 presents the cost including one complex spinal reconstruction procedure and two supporting procedures to treat scoliosis or other spinal deformities and is applied as a one-off cost in the model.

Table 48: Cost (DKK) of Spinal Fusion Surgery

Resource	Cost per unit (DKK)	Units per patient	Source unit cost
Spinal surgery cost	113 924	1	Interaktiv DRG (DG710H) Duchennes muskeldystrofi + (KNAG30) Forreste spondylodese u. fiksation i columna cervialis
Surgery follow-up	40 419	2	DRG takster 2025 08MA18 Efterbehandling af sygdomme i skelet, muskler og bindevæv
Total Cost	194 762		

12. Results

12.1 Base case overview

An overview of the base case is presented in Table 49.

Table 49: Base case overview

Feature	Description
Comparator	GCs alone (SoC)
Type of model	Markov model
Time horizon	50 years (life time)
Treatment line	1st line. Subsequent treatment lines not included.
Measurement and valuation of health effects	Health-related quality of life measured with EQ-5D-5L in a study by Audhya et al. 2023
Costs included	Medicine costs Disease management costs Scoliosis surgery cost
Dosage of medicine	Based on weight
Average time on treatment	Intervention: [redacted] years for givinostat and [redacted]years for GCs Comparator: [redacted]years
Inclusion of waste	Not included
Average time (years) in model health state	
Early ambulatory:	Givinostat+GC: [redacted]GCs[redacted]
Late ambulatory:	Givinostat+GC: [redacted]; GCs [redacted]
Transfer:	Givinostat+GC: [redacted] GCs[redacted]
HTMF, no ventilator:	Givinostat+GC: [redacted]; GCs[redacted]
No HTMF, no ventilator:	Givinostat+GC: [redacted] GCs[redacted]
HTMF, night ventilator:	Givinostat+GC: [redacted]; GCs[redacted]
No HTMF, night ventilator:	Givinostat+GC: [redacted]; GCs[redacted]
Full-time ventilation:	Givinostat+GC: [redacted]; GCs[redacted]

Feature	Description
Death:	Givinostat+GC: [redacted]; GCs: [redacted]

12.1.1 Base case results

The results of the health economic analysis are presented in Table 50. The results indicate that givinostat with concomitant to GC treatment is associated with higher QALYs and life years compared to GC treatment alone. The incremental QALY gain per patient is [redacted] vs [redacted] and [redacted] vs [redacted] for life years gained. Givinostat with concomitant GC treatment is associated with greater total cost compared to GC alone, givinostat is associated with cost-savings in full ventilation costs [redacted] DKK). Givinostat with concomitant GC treatment is associated with increased drug costs. The resulting total incremental cost was [redacted] DKK which yields an ICER [redacted] DKK/QALY.

Table 50: Base case results, discounted estimates

	GCs alone (SoC)	Givinostat+GC	Difference
Drug costs	[redacted]	[redacted]	[redacted]
Early ambulatory costs	[redacted]	[redacted]	[redacted]
Late ambulatory costs	[redacted]	[redacted]	[redacted]
Transfer costs	[redacted]	[redacted]	[redacted]
HTMF, no ventilator costs	[redacted]	[redacted]	[redacted]
No HTMF, no ventilator costs	[redacted]	[redacted]	[redacted]
HTMF, night ventilator costs	[redacted]	[redacted]	[redacted]
No HTMF, night vent costs	[redacted]	[redacted]	[redacted]
Full time ventilation costs	[redacted]	[redacted]	[redacted]
Total health state costs	[redacted]	[redacted]	[redacted]
Cost of spinal fusion	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]
Total life years	[redacted]	[redacted]	[redacted]
Early ambulatory QALYs	[redacted]	[redacted]	[redacted]
Late ambulatory QALYs	[redacted]	[redacted]	[redacted]
Transfers QALYs	[redacted]	[redacted]	[redacted]
HTMF, no ventilator QALYs	[redacted]	[redacted]	[redacted]
No HTMF, no ventilator QALYs	[redacted]	[redacted]	[redacted]
HTMF, night ventilator QALYs	[redacted]	[redacted]	[redacted]
No HTMF, night vent QALYs	[redacted]	[redacted]	[redacted]
Full time ventilation QALYs	[redacted]	[redacted]	[redacted]
Spinal fusion surgery - QALYs lost	[redacted]	[redacted]	[redacted]

	GCs alone (SoC)	Givinostat+GC	Difference
Adverse events - QALYs lost	****	*****	*****
Total QALYs	****	****	****

Incremental costs per life year gained: [redacted]

Incremental cost per QALY gained (ICER): [redacted]

The model contains the possible functionality to explore the impact of a payment model (see sheet "Financial price-volume model" in accompanying model). The incorporated payment model was a financial price-volume model where the rebate level on list price can be adjusted dependent on the total consumption of givinostat bottles. The impact on the ICER and base case result can be explored.

12.2 Sensitivity analyses

12.2.1 Deterministic sensitivity analyses

Results from the one-way sensitivity analyses are presented in Table 51. Top 10 most sensitive parameters are presented in the tornado diagram Figure 14.

Table 51: One-way sensitivity analyses results

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case			*********	********	********
Compliance of givinostat EPIDYS	Upper value: 100%	Could potentially differ in clinical practice	*********	********	********
	Lower value: 79.1%	95% CI, SE assumed to be 10% of point estimate	*********	********	********
Patient utilities: Audhya et al. (2023) - 1 - Early ambulatory	Upper value: 0.895	Based on 95% CI, test the impact of health state utility values	*********	********	********
	Lower value: 0.661		*********	********	*********

Duvyzat® (givinostat) hazard ratio: To state 2 - Late ambulatory	Upper value: 0.583	Based on 95% CI, test the impact of relative disease progression	*********	********	*********
	Lower value: 0.445		*********	********	********
Patient utilities: Audhya et al. (2023) - 2 - Late ambulatory	Upper value: 0.832	Based on 95% CI, test the impact of health state utility values	*********	********	********
	Lower value: 0.421		*********	********	*********
Patient utilities: Audhya et al. (2023) - 8 – Full time ventilation	Upper value: 0.412	Based on 95% CI, test the impact of health state utility values	*********	********	********
	Lower value: 0.066		*********	********	********
Number of patients discontinued givinostat - EPIDYS	Upper value: 8.372	Could potentially differ in clinical practice 95% CI, SE assumed to be 10% of point estimate	*********	********	********
	Lower value: 5.628		*********	********	*********
Duvyzat® (givinostat) hazard ratio: To state 3 - Transfer	Upper value: 0.583	Based on 95% CI, test the impact of relative disease progression	*********	********	********
	Lower value: 0.445		*********	********	********
Duvyzat® (givinostat) hazard ratio: To state 4 - HTMF, no ventilation	Upper value: 0.583	Based on 95% CI, test the impact of relative disease progression	*********	********	********
	Lower value: 0.445		*********	********	********

Patient utilities: Audhya et al. (2023) - 5 - No HTMF, no ventilation	Upper value: 0.364	Based on 95% CI, test the impact of health state utility values	*********	********	*******
	Lower value: 0.121		*********	********	*******

Figure 14: Deterministic sensitivity analysis tornado diagram: top 10 most sensitive parameters

12.2.2 Probabilistic sensitivity analyses

A probabilistic sensitivity analysis (PSA) was conducted to simultaneously vary multiple parameters, based on their distributions, and re-estimate model outputs.

The probabilistic ICERs per QALY gained for givinostat on top of GCs versus GCs alone, shown in Table 52 were similar to the base-case deterministic results. Scatter plot and cost-effectiveness acceptability curve (CEAC) are shown in Figure 15 and Figure 16, respectively.

Table 52: Probabilistic sensitivity analysis results

Treatment	Givinostat + GCs	GCs alone	Difference
Mean QALYs	****	****	****
Mean costs	*********	********	*********
ICER per QALY			********

Figure 15: Cost-effectiveness scatter plot

Figure 16: Cost-effectiveness acceptability curve

12.3 Scenario analyses

Table 53 presents results from scenario analyses. Worth noting is that some of the scenarios lead to substantial differences in the results. In particular, when including the utility of one caregiver, the ICER decreases to [redacted] and when including two caregivers in the analysis, the ICER decreases to [redacted]

Table 53: Scenario analysis including caregiver utilities

Scenario analysis	Incremental costs (DKK)	Incremental QALYs	ICER (DKK)
Patient population: 50% early and 50 % late ambulatory, 9 years at treatment start, weight 32	[redacted]	[redacted]	[redacted]
Patient QoL: Landfeldt	[redacted]	[redacted]	[redacted]

Caregiver utilities: included (one caregiver)	[redacted]	[redacted]	[redacted]
Caregiver utilities: included (two caregivers)	[redacted]	[redacted]	[redacted]
Patients discontinuing treatment with givinostat: disease progression associated with SOC transitions	[redacted]	[redacted]	[redacted]
GCs treatment distribution: 100% receive deflazacort.	[redacted]	[redacted]	[redacted]
Time horizon: 35 years	[redacted]	[redacted]	[redacted]
Time horizon: 55 years	[redacted]	[redacted]	[redacted]
Transfer state: excluded	[redacted]	[redacted]	[redacted]
Discounting: 0%	[redacted]	[redacted]	[redacted]

13. Budget impact analysis

Number of patients (including assumptions of market share)
The base case health economic model is based on treating an incident population according to label as this reflects the long-term treatment situation. This means that early ambulant DMD boys, stable on GC treatment are expected to receive givinostat as an add on treatment once reaching the age of six years old. According to the Danish registry the incidence of DMD is 5 (RehabiliteringsCenter for Muskelsvind 2024).

It is also expected that following the approval of givinostat, patients from the prevalent pool of ambulant patients, eligible according to the key inclusion criteria in the EPIDYS study will start givinostat treatment. This eligible patient pool is estimated to approximately 17 boys. This means that in the BIM model a mix of incident and prevalent patients will start-up givinostat treatment during the first year and by the end of the second year all eligible prevalent patients are estimated to have started treatment. From year 3 and onwards, only incident patients at age 6 will be initiated on treatment.

The expected number of incident patients eligible for givinostat, and the assumed market uptake for givinostat from year 1–5, is presented in Table 54. The numbers are adjusted for treatment start during the year. In year 1, 9 patients are expected to start treatment, but since treatment will be initiated in different months during the year, the number of patient years is expected to be lower than 9. The first year, the number of patient-years is expected to be 4.5 (i.e., 9 patients treated during 50% of the year).

Table 54: Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share) in patient years

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		

	Year 1	Year 2	Year 3	Year 4	Year 5
Givinostat + GCs	4.5	11.9	8.0	3.0	3.0
GCs alone	0	0	0	0	0
			Non-recommendation		
Givinostat + GCs	0	0	0	0	0
GCs alone	4.5	11.9	8.0	3.0	3.0

Budget impact

Based on above calculation of number of patients using a mix of prevalent and incident patient population year 1–3 and incident population from year 4 and onwards, the expected budget impact of a recommendation is presented in Table 55.

Table 55 Expected budget impact of recommending the medicine for the indication

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
The medicine under consideration is NOT recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact of the recommendation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

14. List of experts

Alfred Peter Born, Senior Hospital Physician, Rigshospitalet, Department of Paediatrics and Adolescent Medicine

John Vissing, Senior Physician, Professor, Rigshospitalet, Department of Neurology

15. References

Aartsma-Rus, A. 2025. Histone deacetylase inhibition with givinostat: a multi-targeted mode of action with the potential to halt the pathological cascade of Duchenne muscular dystrophy. *Front Cell Dev Biol,* 12**,** 1514898.

Aartsma-Rus, A., Ginjaar, I. B. & Bushby, K. 2016. The importance of genetic diagnosis for Duchenne muscular dystrophy. *J Med Genet,* 53**,** 145-51.

Aartsma-Rus, A., Hegde, M., Ben-Omran, T., et al. 2019. Evidence-Based Consensus and Systematic Review on Reducing the Time to Diagnosis of Duchenne Muscular Dystrophy. *J Pediatr,* 204**,** 305-313.e14.

Accogli, G., Ferrante, C., Fanizza, I., et al. 2022. Neuromuscular disorders and transition from pediatric to adult care in a multidisciplinary perspective: a narrative review of the scientific evidence and current debate. *Acta Myol,* 41**,** 188-200.

Action Duchenne. 2018. *The Forgotten Voice – living with Duchenne as a sibling* [Online]. Available: https://www.actionduchenne.org/the-forgotten-voice-living-with-duchenne-as-a-sibling/ [Accessed 30 January 2025].

Anderson, J. L., Head, S. I., Rae, C., et al. 2002. Brain function in Duchenne muscular dystrophy. *Brain,* 125**,** 4-13.

Andreozzi, V., Labisa, P., Mota, M., et al. 2022. Quality of life and informal care burden associated with duchenne muscular dystrophy in Portugal: the COIDUCH study. *Health Qual Life Outcomes,* 20**,** 36.

Andrews, J. G. & Wahl, R. A. 2018. Duchenne and Becker muscular dystrophy in adolescents: current perspectives. *Adolesc Health Med Ther,* 9**,** 53-63.

Annexstad, E. J., Fagerheim, T., Holm, I., et al. 2019. Molecular and Clinical Characteristics of a National Cohort of Paediatric Duchenne Muscular Dystrophy Patients in Norway. *J Neuromuscul Dis,* 6**,** 349-359.

Apkon, S. D., Alman, B., Birnkrant, D. J., et al. 2018. Orthopedic and Surgical Management of the Patient With Duchenne Muscular Dystrophy. *Pediatrics,* 142**,** S82-s89.

Archer, J. E., Gardner, A. C., Roper, H. P., et al. 2016. Duchenne muscular dystrophy: the management of scoliosis. *J Spine Surg,* 2**,** 185-194.

Arora, H., Willcocks, R. J., Lott, D. J., et al. 2018. Longitudinal timed function tests in Duchenne muscular dystrophy: ImagingDMD cohort natural history. *Muscle Nerve,* 58**,** 631-638.

ATS Committee 2002. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med,* 166**,** 111-7.

Audhya, I., Rogula, B., Szabo, S. M., et al. 2023a. Exploring the relationship between North Star Ambulatory Assessment and Health Utilities Index scores in Duchenne muscular dystrophy. *Health Qual Life Outcomes,* 21**,** 76.

Audhya, I. F., Szabo, S. M., Bever, A., et al. 2023b. Estimating health state utilities in Duchenne muscular dystrophy using the health utilities index and EQ-5D-5L. *J Patient Rep Outcomes,* 7**,** 132.

Ayyar Gupta, V., Pitchforth, J. M., Domingos, J., et al. 2023. Determining minimal clinically important differences in the North Star Ambulatory Assessment (NSAA) for patients with Duchenne muscular dystrophy. *PLoS One,* 18**,** e0283669.

Balidemaj, A., Parsamanesh, P. & Vysochyn, M. 2023. Exploring the Dynamics of Caring for a Child With a Terminal Illness of Duchenne Muscular Dystrophy (DMD) and Its Copious Components on the Caregivers. *Cureus,* 15**,** e39597.

Barnard, A. M., Willcocks, R. J., Triplett, W. T., et al. 2020. MR biomarkers predict clinical function in Duchenne muscular dystrophy. *Neurology,* 94**,** e897-e909.

Bell, J. M., Shields, M. D., Watters, J., et al. 2017. Interventions to prevent and treat corticosteroid-induced osteoporosis and prevent osteoporotic fractures in Duchenne muscular dystrophy. *Cochrane Database Syst Rev,* 1**,** Cd010899.

Bello, L., Morgenroth, L. P., Gordish-Dressman, H., et al. 2016. DMD genotypes and loss of ambulation in the CINRG Duchenne Natural History Study. *Neurology,* 87**,** 401-9.

Bendixen, R. M., Lott, D. J., Senesac, C., et al. 2014. Participation in daily life activities and its relationship to strength and functional measures in boys with Duchenne muscular dystrophy. *Disabil Rehabil,* 36**,** 1918-23.

Bettica, P., Petrini, S., D'Oria, V., et al. 2016. Histological effects of givinostat in boys with Duchenne muscular dystrophy. *Neuromuscul Disord,* 26**,** 643-649.

Bever, A., Audhya, I., Szabo, S. M., et al. 2024. "You Take This Day by Day, Come What May": A Qualitative Study of the Psychosocial Impacts of Living with Duchenne Muscular Dystrophy. *Adv Ther,* 41**,** 2460-2476.

Bez Batti Angulski, A., Hosny, N., Cohen, H., et al. 2023. Duchenne muscular dystrophy: disease mechanism and therapeutic strategies. *Front Physiol,* 14**,** 1183101.

Birnkrant, D. J., Bushby, K., Bann, C. M., et al. 2018a. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management. *Lancet Neurol,* 17**,** 251-267.

Birnkrant, D. J., Bushby, K., Bann, C. M., et al. 2018b. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management. *Lancet Neurol,* 17**,** 251-267.

Birnkrant, D. J., Bushby, K., Bann, C. M., et al. 2018c. Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bone health, and orthopaedic management. *Lancet Neurol,* 17**,** 347-361.

Birnkrant, D. J., Bushby, K., Bann, C. M., et al. 2018d. Diagnosis and management of Duchenne muscular dystrophy, part 3: primary care, emergency management, psychosocial care, and transitions of care across the lifespan. *Lancet Neurol,* 17**,** 445-455.

Blake, D. J., Weir, A., Newey, S. E., et al. 2002. Function and genetics of dystrophin and dystrophin-related proteins in muscle. *Physiol Rev,* 82**,** 291-329.

Bonilla, E., Samitt, C. E., Miranda, A. F., et al. 1988. Duchenne muscular dystrophy: deficiency of dystrophin at the muscle cell surface. *Cell,* 54**,** 447-52.

Bresolin, N., Castelli, E., Comi, G. P., et al. 1994. Cognitive impairment in Duchenne muscular dystrophy. *Neuromuscul Disord,* 4**,** 359-69.

Brooke, M. H., Fenichel, G. M., Griggs, R. C., et al. 1989. Duchenne muscular dystrophy: patterns of clinical progression and effects of supportive therapy. *Neurology,* 39**,** 475-81.

Broomfield, J., Abrams, K., Latimer, N., et al. 2023. Natural history of Duchenne muscular dystrophy in the United Kingdom: A descriptive study using the Clinical Practice Research Datalink. *Brain Behav***,** e3331.

Broomfield, J., Hill, M., Chandler, F., et al. 2023b. Developing a Natural History Model for Duchenne Muscular Dystrophy. *Pharmacoecon Open*.

Broomfield, J., Hill, M., Chandler, F., et al. 2024. Developing a Natural History Model for Duchenne Muscular Dystrophy. *Pharmacoecon Open,* 8**,** 79-89.

Broomfield, J., Hill, M., Guglieri, M., et al. 2021. Life Expectancy in Duchenne Muscular Dystrophy: Reproduced Individual Patient Data Meta-analysis. *Neurology,* 97**,** e2304-e2314.

Brown, V., Merikle, E., Johnston, K., et al. 2023. A qualitative study to understand the Duchenne muscular dystrophy experience from the parent/patient perspective. *J Patient Rep Outcomes,* 7**,** 129.

Buckon, C., Sienko, S., Bagley, A., et al. 2016. Can Quantitative Muscle Strength and Functional Motor Ability Differentiate the Influence of Age and Corticosteroids in Ambulatory Boys with Duchenne Muscular Dystrophy? *PLoS Curr,* 8.

Bushby, K. & Connor, E. 2011. Clinical outcome measures for trials in Duchenne muscular dystrophy: report from International Working Group meetings. *Clin Investig (Lond),* 1**,** 1217-1235.

Bushby, K., Finkel, R., Birnkrant, D. J., et al. 2010. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. *Lancet Neurol,* 9**,** 77-93.

Campbell, K. P. & Kahl, S. D. 1989. Association of dystrophin and an integral membrane glycoprotein. *Nature,* 338**,** 259-62.

Castro, D., Evans, J. & Jones, C. 2023. Introduction to the Duchenne Muscular Dystrophy Burden-of-Illness Study Expanded (US AND SPAIN) EE92. *Value Health,* 26(12):S68.

Cavazza, M., Kodra, Y., Armeni, P., et al. 2016. Social/economic costs and health-related quality of life in patients with Duchenne muscular dystrophy in Europe. *Eur J Health Econ,* 17 Suppl 1**,** 19-29.

Cazzaniga, S., Bertini, E., Vita, G., et al. 2018. Italfarmaco Poster: Development of the histone deacetylases inhibitor Givinostat in DuchenneMuscular Dystrophy.

Center for Drug Evaluation and Research. 2020. *Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment Guidance for Industry* [Online]. Available: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/duchenne-muscular-dystrophy-and-related-dystrophinopathies-developing-drugs-treatment-guidance [Accessed 8 April 2024].

Cheuk, D. K., Wong, V., Wraige, E., et al. 2015. Surgery for scoliosis in Duchenne muscular dystrophy. *Cochrane Database Syst Rev,* 2015**,** CD005375.

Cheuk, D. K., Wong, V., Wraige, E., et al. 2007. Surgery for scoliosis in Duchenne muscular dystrophy. *Cochrane Database Syst Rev***,** CD005375.

Childs, A. M., Turner, C., Astin, R., et al. 2024. Development of respiratory care guidelines for Duchenne muscular dystrophy in the UK: key recommendations for clinical practice. *Thorax,* 79**,** 476-485.

Ciafaloni, E., Kumar, A., Liu, K., et al. 2016. Age at onset of first signs or symptoms predicts age at loss of ambulation in Duchenne and Becker Muscular Dystrophy: Data from the MD STARnet. *J Pediatr Rehabil Med,* 9**,** 5-11.

ClinicalTrials.gov. 2023a. *Clinical Study to Evaluate the Efficacy and Safety of Givinostat in Ambulant Patients With Duchenne Muscular Dystrophy* [Online]. Available: https://clinicaltrials.gov/study/NCT02851797 [Accessed 19 Mars 2024].

ClinicalTrials.gov. 2023b. *Givinostat in Duchenne's Muscular Dystrophy Long-term Safety and Tolerability Study* [Online]. Available: https://clinicaltrials.gov/study/NCT03373968 [Accessed 7 November 2023].

ClinicalTrials.gov. 2023c. *A Study to Assess Safety/Tolerability, pk, Effects on Histology, Clinical Parameters of Givinostat in Children With DMD* [Online]. Available: https://clinicaltrials.gov/study/NCT01761292 [Accessed 31 January 2025].

Colussi, C., Mozzetta, C., Gurtner, A., et al. 2008. HDAC2 blockade by nitric oxide and histone deacetylase inhibitors reveals a common target in Duchenne muscular dystrophy treatment. *Proc Natl Acad Sci U S A,* 105**,** 19183-7.

Consalvi, S., Mozzetta, C., Bettica, P., et al. 2013. Preclinical studies in the mdx mouse model of duchenne muscular dystrophy with the histone deacetylase inhibitor givinostat. *Mol Med,* 19**,** 79-87.

Consalvi, S., Saccone, V., Giordani, L., et al. 2011. Histone deacetylase inhibitors in the treatment of muscular dystrophies: epigenetic drugs for genetic diseases. *Mol Med,* 17**,** 457-65.

Crisafulli, S., Sultana, J., Fontana, A., et al. 2020. Global epidemiology of Duchenne muscular dystrophy: an updated systematic review and meta-analysis. *Orphanet J Rare Dis,* 15**,** 141.

Crossnohere, N. L., Fischer, R., Lloyd, A., et al. 2021. Assessing the Appropriateness of the EQ-5D for Duchenne Muscular Dystrophy: A Patient-Centered Study. *Med Decis Making,* 41**,** 209-221.

D-RSC. 2025. *Duchenne Regulatory Science Consortium: Overview* [Online]. Available: https://c-path.org/program/duchenne-regulatory-science-consortium/ [Accessed 14 May 2025].

Delaney, R. & O'Halloran, K. D. 2024. Respiratory performance in Duchenne muscular dystrophy: Clinical manifestations and lessons from animal models. *Exp Physiol,* 109**,** 1426-1445.
DMD Care UK. 2024. *Our working groups* [Online]. Available: https://dmdcareuk.org/working-groups [Accessed 14 June 2024].
Do, L. A., Sedita, L. E., Klimchak, A. C., et al. 2024. Cataloging health state utility estimates for Duchenne muscular dystrophy and related conditions. *Health Qual Life Outcomes,* 22**,** 72.
Donnelly, C. M., Quinlivan, R. M., Herron, A., et al. 2023. A systematic review and qualitative synthesis of the experiences of parents of individuals living with Duchenne muscular dystrophy. *Disabil Rehabil,* 45**,** 1285-1298.
Dowling, P., Swandulla, D. & Ohlendieck, K. 2023. Cellular pathogenesis of Duchenne muscular dystrophy: progressive myofibre degeneration, chronic inflammation, reactive myofibrosis and satellite cell dysfunction. *Eur J Transl Myol,* 33.
Duan, D., Goemans, N., Takeda, S., et al. 2021. Duchenne muscular dystrophy. *Nat Rev Dis Primers,* 7**,** 13.
Duchenne Data Foundation. 2022. *Challenges of Duchenne siblings* [Online]. Available: https://www.duchennedatafoundation.org/duchenne-siblings-challenges/ [Accessed 30 January 2025].
Duchenne UK. 2024. *Transforming our rare reality* [Online]. Available: https://www.duchenneuk.org/wp-content/uploads/2024/09/Transforming-our-rare-reality-Duchenne-UK-September-2024.pdf [Accessed 30 January 2025].
Duchenne UK. 2025a. *Duchenne muscular dystrophy in detail* [Online]. Available: https://www.duchenneuk.org/duchenne-in-detail/ [Accessed 24 February 2025].
Duchenne UK. 2025b. *Project HERCULES* [Online]. Available: https://www.duchenneuk.org/project-hercules/ [Accessed 22 February 2025].
Duffy, M. & Wild, J. 2017. A cognitive approach to persistent complex bereavement disorder (PCBD). *Cogn Behav Ther,* 10:e16.
Duong, T., Canbek, J., Birkmeier, M., et al. 2021. The Minimal Clinical Important Difference (MCID) in Annual Rate of Change of Timed Function Tests in Boys with DMD. *J Neuromuscul Dis,* 8**,** 939-948.
Ekström, A., Kroksmark, A., Törnblom, A., et al. 2024. EE818 Economic burden of Duchenne muscular dystrophy patients: A retrospective observational study using Swedish population-based register data. *Value in Health,* 27.
Emery, A. E. 1991. Population frequencies of inherited neuromuscular diseases--a world survey. *Neuromuscul Disord,* 1**,** 19-29.
Emery, A. E. 2002. The muscular dystrophies. *Lancet,* 359**,** 687-95.
Eriksson, B. M., Peny-Dahlstrand, M., Archenholtz, B., et al. 2024. Intervention with hand orthosis: experience from boys with Duchenne muscular dystrophy and their parents. *Disabil Rehabil,* 46**,** 3432-3439.
Ervasti, J. M. & Campbell, K. P. 1993. A role for the dystrophin-glycoprotein complex as a transmembrane linker between laminin and actin. *J Cell Biol,* 122**,** 809-23.
European Medicines Agency. 2016. *Clinical investigation of medicinal products for the treatment of Duchenne and Becker muscular dystrophy - Scientific guideline* [Online]. Available: https://www.ema.europa.eu/en/clinical-investigation-medicinal-products-treatment-duchenne-becker-muscular-dystrophy-scientific-guideline [Accessed 8 April 2024].
European Medicines Agency. 2024a. *EMA recommends non-renewal of authorisation of Duchenne muscular dystrophy medicine Translarna* [Online]. Available: https://www.ema.europa.eu/en/news/ema-recommends-non-renewal-authorisation-duchenne-muscular-dystrophy-medicine-translarna-0 [Accessed 30 January 2025].

European Medicines Agency. 2024b. *Summary of Product Characteristics - Agamree* [Online]. Available: https://www.ema.europa.eu/en/documents/product-information/agamree-epar-product-information_en.pdf [Accessed 11 November 2024].
European Medicines Agency. 2025. *Duvyzat®(Givinostat) Summary of Product Characteristics* [Online]. Available: TBA [Accessed TBA].
Evans, J., Cawson, M. & Hubberstey, H. 2020. DMD UK: Quantifying the socioeconomic cost of Duchenne Muscular Dystrophy in the UK. *Report V1.0 (from University of Chester)*.
FDA. 2024. *Duzyvat prescribing information 03/2024* [Online]. Available: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/217865Orig1s000lbl.pdf [Accessed 15 May 2024].
Felisari, G., Martinelli Boneschi, F., Bardoni, A., et al. 2000. Loss of Dp140 dystrophin isoform and intellectual impairment in Duchenne dystrophy. *Neurology,* 55**,** 559-64.
Finkel, R., Phan, H., Alessi, F., et al. 2025. Efficacy of givinostat in the off-target population of EPIDYS: a subgroup analysis. *Presented at the MDA Clinical & Scientific Conference March 16-19, Dallas, Texas*.
Giordano, C., Mojumdar, K., Liang, F., et al. 2015. Toll-like receptor 4 ablation in mdx mice reveals innate immunity as a therapeutic target in Duchenne muscular dystrophy. *Hum Mol Genet,* 24**,** 2147-62.
Giuliani, G., Rosina, M. & Reggio, A. 2022. Signaling pathways regulating the fate of fibro/adipogenic progenitors (FAPs) in skeletal muscle regeneration and disease. *Febs j,* 289**,** 6484-6517.
Gloss, D., Moxley, R. T., 3rd, Ashwal, S., et al. 2016. Practice guideline update summary: Corticosteroid treatment of Duchenne muscular dystrophy: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology,* 86**,** 465-72.
Guiraud, S., Chen, H., Burns, D. T., et al. 2015. Advances in genetic therapeutic strategies for Duchenne muscular dystrophy. *Exp Physiol,* 100**,** 1458-67.
Guyot, P., Ades, A. E., Ouwens, M. J., et al. 2012. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. *BMC Med Res Methodol,* 12**,** 9.
Hagiwara, Y., Shiroiwa, T., Shimozuma, K., et al. 2018. Impact of Adverse Events on Health Utility and Health-Related Quality of Life in Patients Receiving First-Line Chemotherapy for Metastatic Breast Cancer: Results from the SELECT BC Study. *Pharmacoeconomics,* 36**,** 215-223.
Henricson, E. K., Abresch, R. T., Cnaan, A., et al. 2013. The cooperative international neuromuscular research group Duchenne natural history study: glucocorticoid treatment preserves clinically meaningful functional milestones and reduces rate of disease progression as measured by manual muscle testing and other commonly used clinical trial outcome measures. *Muscle Nerve,* 48**,** 55-67.
Hoffman, E. P., Brown, R. H., Jr. & Kunkel, L. M. 1987. Dystrophin: the protein product of the Duchenne muscular dystrophy locus. *Cell,* 51**,** 919-28.
Houwen-van Opstal, S. L. S., Heutinck, L., Jansen, M., et al. 2021. Occurrence of symptoms in different stages of Duchenne muscular dystrophy and their impact on social participation. *Muscle Nerve,* 64**,** 701-709.
Huang, C., Peng, J., Lee, P. M. Y., et al. 2024. Sibling Death in Childhood and Early Adulthood and Risk of Early-Onset Cardiovascular Disease. *JAMA Netw Open,* 7**,** e2350814.
Humbertclaude, V., Hamroun, D., Bezzou, K., et al. 2012. Motor and respiratory heterogeneity in Duchenne patients: implication for clinical trials. *Eur J Paediatr Neurol,* 16**,** 149-60.

Italfarmaco 2019. Study 43 Clinical Study Report V1.0. *Data on file*.
Italfarmaco 2020. Study 48 (EPIDYS) Protocol. *Data on file*.
Italfarmaco 2022a. Study 48 (EPIDYS) Clinical Study Report. *Data on file*.
Italfarmaco 2022b. Study 48 (EPIDYS) Statistical Analysis Plan. Version: Final 6.0. *Data on file*.
Italfarmaco 2023. Study 51 Protocol: V6.0 Final. 17 April 2023. *Data on file*.
Italfarmaco 2024a. Excerpt from D120 EMA responses. *Data on file*.
Italfarmaco 2024b. HTA Advisory Board (20 June 2024). *Data on file*.
Italfarmaco 2024c. Interview with leading clinical expert, SME - Alfred Peter Born (Senior Hospital Physician , Rigshospitalet, Department of Paediatrics and Adolescent Medicine). *Data on File*.
Italfarmaco 2024d. Interview with leading clinical expert, SME - Ellen Annexstad (Senior Consultant in Pediatrics, MD, PhD, at Oslo University Hospital) *Data on File*.
Italfarmaco 2024e. Interview with leading clinical expert, SME - John Vissing (Senior Physician, Professor, Rigshospitalet, Department of Neurology). *Data on File*.
Italfarmaco 2024f. Interview with leading clinical expert, SME - Sean Wallace (Senior Consultant in Pediatrics; MD, PhD, Oslo University Hospital). *Data on file*.
Italfarmaco 2024g. Interview with leading clinical expert, SME - Trine Haug Popperud (Senior Consultant in Neurology, MD, PhD, at Oslo University Hospital). *Data on File*.
Italfarmaco 2024h. North Star Summary Data. *Data on file*.
Italfarmaco 2024i. SLR addendum: Clinical database screening_240513. *Data on file*.
Italfarmaco 2024j. SLR addendum: Clinical database screening_241113. *Data on file*.
Italfarmaco 2024k. SLR addendum: Clinical FTR screening_240611. *Data on file*.
Italfarmaco 2024l. SLR addendum: Clinical FTR screening_241121. *Data on file*.
Italfarmaco 2024m. SLR addendum: Grey literature screening_Clinical and costs. *Data on file*.
Italfarmaco 2024n. SLR addendum: Grey literature screening_Clinical and costs_241111. *Data on file*.
Italfarmaco 2024o. SLR addendum: Utilities Cost Economic database screening_240513. *Data on file*.
Italfarmaco 2024p. SLR addendum: Utilities Cost Economic database screening_241113. *Data on file*.
Italfarmaco 2024q. SLR addendum: Utilities Cost Economic FTR screening_240606. *Data on file*.
Italfarmaco 2024r. SLR addendum: Utilities Cost Economic FTR screening_241121. *Data on file*.
Italfarmaco 2024s. Study 51 Clinical Study Report. 5th interim analysis 31-Dec-2023. Version 1.0, 25 June 2024. *Data on file*.
Italfarmaco 2025a. Analysis from the December 2023 data cut of patients in EPIDYS, Study 43 and OLE who matched the key inclusion criteria for the EPIDYS study and had received givinostat from study entry. *Data on file*.
Italfarmaco 2025b. Swedish registry study. *Data on file*.
Italfarmaco SpA 2020. Study 48 (EPIDYS) Protocol. Section 6.1. *Data on file*.
Italfarmaco UK 2024. Analysing DMD through HES. *Data on file*.
Janssen, M. M., Hendriks, J. C., Geurts, A. C., et al. 2016. Variables associated with upper extremity function in patients with Duchenne muscular dystrophy. *J Neurol,* 263**,** 1810-8.
Kodippili, K. & Rudnicki, M. A. 2023. Satellite cell contribution to disease pathology in Duchenne muscular dystrophy. *Front Physiol,* 14**,** 1180980.
Koeks, Z., Bladen, C. L., Salgado, D., et al. 2017. Clinical Outcomes in Duchenne Muscular Dystrophy: A Study of 5345 Patients from the TREAT-NMD DMD Global Database. Supplementary Material. *J Neuromuscul Dis,* 4**,** 293-306.

Koumbourlis, A. C. 2006. Scoliosis and the respiratory system. *Paediatr Respir Rev,* 7**,** 152-60.
Lamb, Y. N. 2024. Givinostat: First Approval. *Drugs,* 84**,** 849-856.
Landfeldt, E., Alfredsson, L., Straub, V., et al. 2017a. Economic Evaluation in Duchenne Muscular Dystrophy: Model Frameworks for Cost-Effectiveness Analysis. *Pharmacoeconomics,* 35**,** 249-258.
Landfeldt, E., Eagle, M., Straub, V., et al. 2017b. Mortality Cost of Duchenne Muscular Dystrophy. *Global and Regional Health Technology Assessment,* 4**,** 100-103.
Landfeldt, E., Edström, J., Buccella, F., et al. 2018. Duchenne muscular dystrophy and caregiver burden: a systematic review. *Dev Med Child Neurol,* 60**,** 987-996.
Landfeldt, E., Lindgren, P., Bell, C. F., et al. 2016a. Health-related quality of life in patients with Duchenne muscular dystrophy: a multinational, cross-sectional study. *Dev Med Child Neurol,* 58**,** 508-15.
Landfeldt, E., Lindgren, P., Bell, C. F., et al. 2016b. Quantifying the burden of caregiving in Duchenne muscular dystrophy. *J Neurol,* 263**,** 906-915.
Landfeldt, E., Lindgren, P., Bell, C. F., et al. 2014. The burden of Duchenne muscular dystrophy: an international, cross-sectional study. *Neurology,* 83**,** 529-36.
Landfeldt, E., Mayhew, A., Eagle, M., et al. 2015. Development and psychometric analysis of the Duchenne muscular dystrophy Functional Ability Self-Assessment Tool (DMDSAT). *Neuromuscul Disord,* 25**,** 937-44.
Landfeldt, E., Thompson, R., Sejersen, T., et al. 2020. Life expectancy at birth in Duchenne muscular dystrophy: a systematic review and meta-analysis. *Eur J Epidemiol,* 35**,** 643-653.
Landfeldt, E., Zhang, R., Childs, A. M., et al. 2022. Assessment of face validity of a disease model of nonsense mutation Duchenne muscular dystrophy: a multi-national Delphi panel study. *J Med Econ,* 25**,** 808-816.
Latimer, N. 2013. NICE DSU technical support document 14: survival analysis for economic evaluations alongside clinical trials-extrapolation with patient-level data.
Le, S., Yu, M., Hovan, L., et al. 2018. Dystrophin As a Molecular Shock Absorber. *ACS Nano,* 12**,** 12140-12148.
Levine, H., Goldfarb, I., Katz, J., et al. 2023. Pulmonary function tests for evaluating the severity of Duchenne muscular dystrophy disease. *Acta Paediatr,* 112**,** 854-860.
Licandro, S. A., Crippa, L., Pomarico, R., et al. 2021. The pan HDAC inhibitor Givinostat improves muscle function and histological parameters in two Duchenne muscular dystrophy murine models expressing different haplotypes of the LTBP4 gene. *Skelet Muscle,* 11**,** 19.
Licciardi, P. V. & Karagiannis, T. C. 2012. Regulation of immune responses by histone deacetylase inhibitors. *ISRN Hematol,* 2012**,** 690901.
Łoboda, A., & Dulak, J. 2020. Muscle and cardiac therapeutic strategies for Duchenne muscular dystrophy: past, present, and future. *Pharmacol Rep,* 72**,** 1227-1263.
LoMauro, A., D'Angelo, M. G. & Aliverti, A. 2015. Assessment and management of respiratory function in patients with Duchenne muscular dystrophy: current and emerging options. *Ther Clin Risk Manag,* 11**,** 1475-88.
Lynn, S., Aartsma-Rus, A., Bushby, K., et al. 2015. Measuring clinical effectiveness of medicinal products for the treatment of Duchenne muscular dystrophy. *Neuromuscul Disord,* 25**,** 96-105.
Magliano, L., D'Angelo, M. G., Vita, G., et al. 2014. Psychological and practical difficulties among parents and healthy siblings of children with Duchenne vs. Becker muscular dystrophy: an Italian comparative study. *Acta Myol,* 33**,** 136-43.
Magliano, L., Patalano, M., Sagliocchi, A., et al. 2015. Burden, professional support, and social network in families of children and young adults with muscular dystrophies. *Muscle Nerve,* 52**,** 13-21.

Manzur, A. Y., Kuntzer, T., Pike, M., et al. 2008. Glucocorticoid corticosteroids for Duchenne muscular dystrophy. *Cochrane Database Syst Rev*, CD003725.
Marrone, A. K. & Shcherbata, H. R. 2011. Dystrophin Orchestrates the Epigenetic Profile of Muscle Cells Via miRNAs. *Front Genet,* 2, 64.
Matsumura, K. & Campbell, K. P. 1994. Dystrophin-glycoprotein complex: its role in the molecular pathogenesis of muscular dystrophies. *Muscle Nerve,* 17, 2-15.
Matthews, E., Brassington, R., Kuntzer, T., et al. 2016. Corticosteroids for the treatment of Duchenne muscular dystrophy. *Cochrane Database Syst Rev,* 2016, Cd003725.
Matza, L. S., Chung, K., Van Brunt, K., et al. 2014. Health state utilities for skeletal-related events secondary to bone metastases. *Eur J Health Econ,* 15, 7-18.
Mayer, O. H. 2019. Pulmonary function and clinical correlation in DMD. *Paediatr Respir Rev,* 30, 13-15.
Mayo, A. L., Craven, B. C., McAdam, L. C., et al. 2012. Bone health in boys with Duchenne Muscular Dystrophy on long-term daily deflazacort therapy. *Neuromuscul Disord,* 22, 1040-5.
Mazzone, E. S., Coratti, G., Sormani, M. P., et al. 2016. Timed Rise from Floor as a Predictor of Disease Progression in Duchenne Muscular Dystrophy: An Observational Study. *PLoS One,* 11, e0151445.
McAdam, L., Alessi, F., Gomez, N. M., et al. 2025. Patient-Reported Outcomes From a Phase 3 Study of Givinostat in Patients With Duchenne Muscular Dystrophy. *Presented at the ISPOR Conference, Montreal, Canada*.
McDonald, C., Laverty, C. G., Finanger, E. L., et al. 2025. Givinostat Effect on Respiratory Function in Duchenne Muscular Dystrophy Before and After Ambulation Loss: Results from EPIDYS, OLE, and PRO-DMD-01. *Presented at the MDA Clinical & Scientific Conference March 16-19, Dallas, Texas 2025*
McDonald, C., Muntoni, F. & Marden, J. 2022a. Development and evaluation of a time to event endpoint for clinical trials in Duchenne muscular dystrophy (DMD). *Neuromuscul Disord,* 32:S69 (P67).
McDonald, C. M. 2018. Timed function tests have withstood the test of time as clinically meaningful and responsive endpoints in duchenne muscular dystrophy. *Muscle Nerve,* 58, 614-617.
McDonald, C. M., Abresch, R. T., Carter, G. T., et al. 1995. Profiles of neuromuscular diseases. Duchenne muscular dystrophy. *Am J Phys Med Rehabil,* 74, S70-92.
McDonald, C. M., Campbell, C., Torricelli, R. E., et al. 2017. Ataluren in patients with nonsense mutation Duchenne muscular dystrophy (ACT DMD): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet,* 390, 1489-1498.
McDonald, C. M., Henricson, E. H., Leinonen, M., et al. 2021. Evolution of time to stand velocity in glucocorticoid-using and non-using patients with DMD. Poster presented at Parent Project Muscular Dystrophy Annual Conference; 23–26 June 2021; Virtual.
McDonald, C. M., Henricson, E. K., Abresch, R. T., et al. 2018. Long-term effects of glucocorticoids on function, quality of life, and survival in patients with Duchenne muscular dystrophy: a prospective cohort study. *Lancet,* 391, 451-461.
McDonald, C. M., Henricson, E. K., Abresch, R. T., et al. 2013a. The 6-minute walk test and other endpoints in Duchenne muscular dystrophy: longitudinal natural history observations over 48 weeks from a multicenter study. *Muscle Nerve,* 48, 343-56.
McDonald, C. M., Henricson, E. K., Abresch, R. T., et al. 2013b. The cooperative international neuromuscular research group Duchenne natural history study--a

longitudinal investigation in the era of glucocorticoid therapy: design of protocol and the methods used. *Muscle Nerve,* 48**,** 32-54.
McDonald, C. M., Henricson, E. K., Han, J. J., et al. 2010a. The 6-minute walk test in Duchenne/Becker muscular dystrophy: longitudinal observations. *Muscle Nerve,* 42**,** 966-74.
McDonald, C. M., McDonald, D. A., Bagley, A., et al. 2010b. Relationship between clinical outcome measures and parent proxy reports of health-related quality of life in ambulatory children with Duchenne muscular dystrophy. *J Child Neurol,* 25**,** 1130-44.
McDonald, C. M., Muntoni, F., Penematsa, V., et al. 2022b. Ataluren delays loss of ambulation and respiratory decline in nonsense mutation Duchenne muscular dystrophy patients. *J Comp Eff Res,* 11**,** 139-155.
McDonald, C. M., Signorovitch, J., Mercuri, E., et al. 2024. Functional trajectories before and after loss of ambulation in Duchenne muscular dystrophy and implications for clinical trials. *PLoS One,* 19**,** e0304099.
Medicinrådet. 2024. *Key figures including general mortality within the Danish population* [Online]. Available: https://filer.medicinraadet.dk/media/r3rpnsff/key-figures-including-general-mortality-within-the-danish-population.xlsx [Accessed 22 April 2024].
Medicinrådet. 2025a. *Ansøgningsproces for nye lægemidler og indikationsudvidelser* [Online]. Available: https://medicinraadet.dk/ansogning/om-ansogning-generelt [Accessed 14 March 2025].
Medicinrådet. 2025b. *Vamorolone (Agamree)* [Online]. Available: https://medicinraadet.dk/igangvaerende-vurderinger/laegemidler-og-indikationsudvidelser/vamorolone-agamree-duchennes-muskeldystrofi-dmd [Accessed 13 March 2025].
Mercuri, E., Brogna, C., Mah, J. K., et al. 2023a. Givinostat in DMD: results of the Epidys Study with particular attention to NSAA. *Poster presented at the 2023 MDA Clinical & Scientific Conference, Dallas, USA, 19-21 March 2023*.
Mercuri, E., Brogna, C., Zaidman, C., et al. 2024a. Givinostat Study in DMD: supportive results. *MDA Clin. Sci. Conf*.
Mercuri, E., Osorio, A. N., Muntoni, F., et al. 2023b. Safety and effectiveness of ataluren in patients with nonsense mutation DMD in the STRIDE Registry compared with the CINRG Duchenne Natural History Study (2015-2022): 2022 interim analysis. *J Neurol,* 270**,** 3896-3913.
Mercuri, E., Signorovitch, J. E., Swallow, E., et al. 2016. Categorizing natural history trajectories of ambulatory function measured by the 6-minute walk distance in patients with Duchenne muscular dystrophy. *Neuromuscul Disord,* 26**,** 576-83.
Mercuri, E., Vilchez, J. J., Boespflug-Tanguy, O., et al. 2024b. Safety and efficacy of givinostat in boys with Duchenne muscular dystrophy (EPIDYS): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Neurol,* 23**,** 393-403.
Mercuri, E., Vilchez, J. J., Boespflug-Tanguy, O., et al. 2024c. Safety and efficacy of givinostat in boys with Duchenne muscular dystrophy (EPIDYS): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Supplementary Appendix. *Lancet Neurol,* 23.
Mercuri, E., Vilchez, J. J., Boesplug-Tanguy, O., et al. 2024d. Safety and efficacy of givinostat in Duchenne muscular dystrophy: a randomised, doble-blind, placebo-controlled, multicentre Phase 3 study. *Lancet Neurology*.
Minetti, G. C., Colussi, C., Adami, R., et al. 2006. Functional and morphological recovery of dystrophic muscles in mice treated with deacetylase inhibitors. *Nat Med,* 12**,** 1147-50.

Molinari, S., Imbriano, C., Moresi, V., et al. 2023. Histone deacetylase functions and therapeutic implications for adult skeletal muscle metabolism. *Front Mol Biosci,* 10**,** 1130183.
Mozzetta, C., Sartorelli, V., Steinkuhler, C., et al. 2024. HDAC inhibitors as pharmacological treatment for Duchenne muscular dystrophy: a discovery journey from bench to patients. *Trends Mol Med,* 30**,** 278-294.
Muntoni, F., Domingos, J., Manzur, A. Y., et al. 2019. Categorising trajectories and individual item changes of the North Star Ambulatory Assessment in patients with Duchenne muscular dystrophy. *PLoS One,* 14**,** e0221097.
Muntoni, F., Goemans, N., Posner, N., et al. 2023. *PCR28 Characterization of Patients with Duchenne Muscular Dystrophy across Previously Developed Health States* [Online]. Available: https://www.valueinhealthjournal.com/article/S1098-3015(23)01908-3/fulltext [Accessed 15 December 2025].
Muscular Dystrophy Assoc. 2024. *School accomodation recommendations* [Online]. Available: https://www.mda.org/sites/default/files/Guide_SchoolAccommodations-DMD2.pdf [Accessed 1 May 2024].
Muscular Dystrophy UK. 2025. *Northstar programme* [Online]. Available: https://www.musculardystrophyuk.org/research/current-projects/northstar-programme/ [Accessed 6 March 2025].
Nair, K. S., Lott, D. J., Forbes, S. C., et al. 2022. Step Activity Monitoring in Boys with Duchenne Muscular Dystrophy and its Correlation with Magnetic Resonance Measures and Functional Performance. *J Neuromuscul Dis,* 9**,** 423-436.
Nart, L., Desikan, M., Pietrusz, A., et al. 2024. Neurodiversity, treatment compliance and survival in adults with Duchenne muscular dystrophy: a single-centre retrospective cohort review. *Neuromuscul Disord,* 35**,** 13-18.
NICE. 2023a. *Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene: Highly specialised technologies guidance* [Online]. Available: https://www.nice.org.uk/guidance/hst22 [Accessed 22 Feburary 2024].
NICE. 2023b. *Vamorolone for treating Duchenne muscular dystrophy [ID4024] Response to stakeholder organisation comments on the draft remit and draft scope* [Online]. Available: https://www.nice.org.uk/guidance/gid-ta11135/documents/scope-consultation-comments-and-responses-2 [Accessed 9 April 2024].
NICE. 2025. *Vamorolone for treating Duchenne muscular dystrophy* [Online]. Available: https://www.nice.org.uk/guidance/TA1031 [Accessed 4 March 2025].
Nigro, G., Comi, L. I., Politano, L., et al. 1990. The incidence and evolution of cardiomyopathy in Duchenne muscular dystrophy. *Int J Cardiol,* 26**,** 271-7.
Nowak, K. J. & Davies, K. E. 2004. Duchenne muscular dystrophy and dystrophin: pathogenesis and opportunities for treatment. *EMBO Rep,* 5**,** 872-6.
Okubo, M., Goto, K., Komaki, H., et al. 2017. Comprehensive analysis for genetic diagnosis of Dystrophinopathies in Japan. *Orphanet J Rare Dis,* 12**,** 149.
Orso, M., Migliore, A., Polistena, B., et al. 2023. Duchenne muscular dystrophy in Italy: A systematic review of epidemiology, quality of life, treatment adherence, and economic impact. *PLoS One,* 18**,** e0287774.
Oslo Economics. 2023. *Samfunnskostnader forbundet med Duchennes muskeldystrofi i Norge* [Online]. Available: https://osloeconomics.no/wp-content/uploads/2023/01/Samfunnskostnader-forbundet-med-Duchennes-muskeldystrofi-i-Norge.pdf [Accessed 5 December 2024].
Osseni, A., Ravel-Chapuis, A., Belotti, E., et al. 2022. Pharmacological inhibition of HDAC6 improves muscle phenotypes in dystrophin-deficient mice by downregulating TGF-beta via Smad3 acetylation. *Nat Commun,* 13**,** 7108.

Pascual-Morena, C., Cavero-Redondo, I., Alvarez-Bueno, C., et al. 2020. Restorative treatments of dystrophin expression in Duchenne muscular dystrophy: A systematic review. *Ann Clin Transl Neurol,* 7**,** 1738-1752.

Passamano, L., Taglia, A., Palladino, A., et al. 2012. Improvement of survival in Duchenne Muscular Dystrophy: retrospective analysis of 835 patients. *Acta Myol,* 31**,** 121-5.

Petrof, B. J., Shrager, J. B., Stedman, H. H., et al. 1993. Dystrophin protects the sarcolemma from stresses developed during muscle contraction. *Proc Natl Acad Sci U S A,* 90**,** 3710-4.

Pfizer UK 2024a. Caregiver vignette study in Duchenne muscular dystrophy. Version 3, 3 June 2024. With grateful thanks to Pfizer UK who commissioned this report and shared it with ITF Pharma UK. *Data on file*.

Pfizer UK 2024b. Qualitative interview study with caregivers who care for a person with DMD. Version 3.0; 29 May 2024. With grateful thanks to Pfizer UK who commissioned this report and shared it with ITF Pharma UK. *Data on file*.

Phillippo D, A. A., Dias S 2016. NICE DSU Technical Support Document 18: Methods for Population-Adjusted Comparison in Submissions to NICE: Report by the Decision Support Unit.

Phillippo, D. M., Ades, A. E., Dias, S., et al. 2018. Methods for Population-Adjusted Indirect Comparisons in Health Technology Appraisal. *Med Decis Making,* 38**,** 200-211.

Phillips, M. F., Quinlivan, R. C., Edwards, R. H., et al. 2001. Changes in spirometry over time as a prognostic marker in patients with Duchenne muscular dystrophy. *Am J Respir Crit Care Med,* 164**,** 2191-4.

Pietrusz, A. 2024. Natural history of DMD cohort attending Neuromuscular Service National Hospital for Neurology and Neurosurgery, Queen Square, London. *PowerPoint presentation, Data on file*.

Pietrusz, A. 2025. *A natural history study of adults with Duchenne Muscular Dystrophy living in the UK. A thesis submission to University College London for the degree of Doctor of Philosophy (PhD), currently under embargo* [Online]. Available: https://discovery.ucl.ac.uk/id/eprint/10203022/ [Accessed August 2025].

Pietrusz, A., Astin, R., Guglieri, M., et al. 2023. The effect of corticosteroid treatment on pulmonary function in adults with Duchenne muscular dystrophy. *Presented at: the 28th International Annual Congress of the World Muscle Society (WMS), Charleston, South Carolina, US.,* 33**,** pp.S106-S107.

Porteous, D., Davies, B., English, C., et al. 2021. An Integrative Review Exploring Psycho-Social Impacts and Therapeutic Interventions for Parent Caregivers of Young People Living with Duchenne's Muscular Dystrophy. *Children (Basel),* 8.

Quak, Z. X., Tan, S. M. L., Tan, K. B., et al. 2023. A manifesting female carrier of Duchenne muscular dystrophy: Importance of genetics for the dystrophinopathies. *Singapore Med J,* 64**,** 81-87.

Rae, M. G. & O'Malley, D. 2016. Cognitive dysfunction in Duchenne muscular dystrophy: a possible role for neuromodulatory immune molecules. *J Neurophysiol,* 116**,** 1304-15.

Rall, S. & Grimm, T. 2012. Survival in Duchenne muscular dystrophy. *Acta Myol,* 31**,** 117-20.

RehabiliteringsCenter for Muskelsvind. 2024. *Duchennes muskeldystrofi* [Online]. Available: https://rcfm.dk/diagnose/duchenns-muskeldystrofi-dmd/ [Accessed 19 May 2024].

RehabiliteringsCenter for Muskelsvind. 2025. *Duchennes muskeldystrofi (DMD)* [Online]. Available: https://rcfm.dk/diagnose/duchenns-muskeldystrofi-dmd/ [Accessed 13 March 2025].

Reid, A. L. & Alexander, M. S. 2021. The Interplay of Mitophagy and Inflammation in Duchenne Muscular Dystrophy. *Life (Basel),* 11.
Ren, S., Fu, X., Guo, W., et al. 2024. Profound cellular defects attribute to muscular pathogenesis in the rhesus monkey model of Duchenne muscular dystrophy. *Cell,* 187**,** 6669-6686 e16.
Ricci, G., Bello, L., Torri, F., et al. 2022. Therapeutic opportunities and clinical outcome measures in Duchenne muscular dystrophy. *Neurol Sci,* 43**,** 625-633.
Ricotti, V., Ridout, D. A., Pane, M., et al. 2016. The NorthStar Ambulatory Assessment in Duchenne muscular dystrophy: considerations for the design of clinical trials. *J Neurol Neurosurg Psychiatry,* 87**,** 149-55.
Roberts, J., Hickey, D., Sharer, S., et al. 2024. Healthcare resource utilisation (HCRU) by patients with Duchenne Muscular Dystrophy (DMD) using UK patient level data (EE198). *Presented at ISPOR Europe 2024. Barcelona: 2024*.
Rooney, W. D., Berlow, Y. A., Triplett, W. T., et al. 2020. Modeling disease trajectory in Duchenne muscular dystrophy. *Neurology,* 94**,** e1622-e1633.
Rudolfsen, J. H., Vissing, J., Werlauff, U., et al. 2024. Burden of Disease of Duchenne Muscular Dystrophy in Denmark - A National Register-Based Study of Individuals with Duchenne Muscular Dystrophy and their Closest Relatives. *J Neuromuscul Dis*.
Rugowska, A., Starosta, A. & Konieczny, P. 2021. Epigenetic modifications in muscle regeneration and progression of Duchenne muscular dystrophy. *Clin Epigenetics,* 13**,** 13.
Ryder, S., Leadley, R. M., Armstrong, N., et al. 2017. The burden, epidemiology, costs and treatment for Duchenne muscular dystrophy: an evidence review. *Orphanet J Rare Dis,* 12**,** 79.
Saccone, V., Consalvi, S., Giordani, L., et al. 2014. HDAC-regulated myomiRs control BAF60 variant exchange and direct the functional phenotype of fibro-adipogenic progenitors in dystrophic muscles. *Genes Dev,* 28**,** 841-57.
Sandonà, M., Cavioli, G., Renzini, A., et al. 2023a. Histone Deacetylases: Molecular Mechanisms and Therapeutic Implications for Muscular Dystrophies. *Int J Mol Sci,* 24.
Sandonà, M., Consalvi, S., Tucciarone, L., et al. 2016. HDAC inhibitors for muscular dystrophies: progress and prospects. *Expert Opin Orphan Drugs,* 4**,** 125-7.
Sandonà, M., Esposito, F., Cargnoni, A., et al. 2023b. Amniotic Membrane-Derived Stromal Cells Release Extracellular Vesicles That Favor Regeneration of Dystrophic Skeletal Muscles. *Int J Mol Sci,* 24.
Sawnani, H., Horn, P. S., Wong, B., et al. 2019. Comparison of Pulmonary Function Decline in Steroid-Treated and Steroid-Naive Patients with Duchenne Muscular Dystrophy. *J Pediatr,* 210**,** 194-200 e2.
Schreiber-Katz, O., Klug, C., Thiele, S., et al. 2014. Comparative cost of illness analysis and assessment of health care burden of Duchenne and Becker muscular dystrophies in Germany. *Orphanet J Rare Dis,* 9**,** 210.
Schultz, T. I., Raucci, F. J., Jr. & Salloum, F. N. 2022. Cardiovascular Disease in Duchenne Muscular Dystrophy: Overview and Insight Into Novel Therapeutic Targets. *JACC Basic Transl Sci,* 7**,** 608-625.
Schwartz, C. E., Stark, R. B., Audhya, I. F., et al. 2021. Characterizing the quality-of-life impact of Duchenne muscular dystrophy on caregivers: a case-control investigation. *J Patient Rep Outcomes,* 5**,** 124.
SDU.dk. 2025. *Vi bliver højere og tungere* [Online]. Available: https://www.sdu.dk/da/sif/ugens_tal/35_2022 [Accessed 15 March 2025].
Soim, A., Lamb, M. M. & Campbell, K. 2016. A cross-sectional study of school experiences of boys with Duchenne and Becker Muscular Dystrophy. *Phys Disabil Educ Relat Serv,* 35(2):1–22.

Stark, A. E. 2015. Determinants of the incidence of Duchenne muscular dystrophy. *Ann Transl Med,* 3**,** 287.
Strober, J., Ishigaki, K. & Merla, V. 2023. Healthcare resource utilization for pediatric and adolescent Duchenne Muscular Dystrophy patients: analysis of real-world data. *Value Health,* 26 (12, Supplement):S529.
Sullivan, P. W., Slejko, J. F., Sculpher, M. J., et al. 2011. Catalogue of EQ-5D scores for the United Kingdom. *Med Decis Making,* 31**,** 800-4.
Sundhed.dk. 2025. *Danish growth charts, 4-17 years* [Online]. Available: https://www.sundhed.dk/borger/patienthaandbogen/boern/illustrationer/tegning/ [Accessed 15 March 2025].
Szabo, S., Audhya, I. & Bever, A. 2023a. The Association between Patient-and Caregiver-Reported Utility Values in Duchenne Muscular Dystrophy (DMD) (P31). *Value Health,* 26(6):S7.
Szabo, S., Audhya, I., Griffin, E., et al. 2023b. *PCR192 Content Validity of the EQ-5D and Health Utilities Index (HUI) to Assess Health-Related Quality-of-Life (HRQoL) Impact in Duchenne Muscular Dystrophy (DMD)* [Online]. Available: https://www.valueinhealthjournal.com/article/S1098-3015(23)05759-5/fulltext [Accessed 15 December 2025].
Szabo, S. M., Audhya, I. F., Rogula, B., et al. 2022. Factors associated with the health-related quality of life among people with Duchenne muscular dystrophy: a study using the Health Utilities Index (HUI). *Health Qual Life Outcomes,* 20**,** 93.
Tierney, J. F., Stewart, L. A., Ghersi, D., et al. 2007. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials,* 8**,** 16.
Vandenborne, K. 2023. *Givinostat in DMD: results of the Epidys Study with particular attention to MR measures of muscle fat fraction* [Online]. Chicago: MDA. Available: https://www.mdaconference.org/abstract-library/givinostat-in-dmd-results-of-the-epidys-study-with-particular-attention-to-mr-measures-of-muscle-fat-fraction/ [Accessed].
Vucinic, D., Nascimento, A., Finkel, R., et al. 2024. Short term and long term safety profile of Givinostat in Duchenne Muscular Dystrophy. *Neuromuscul Disord,* 43(Supplement 1) 409P.
Walter, M. C. & Reilich, P. 2017. Recent developments in Duchenne muscular dystrophy: facts and numbers. *J Cachexia Sarcopenia Muscle,* 8**,** 681-685.
Wasilewska, E., Malgorzewicz, S., Sobierajska-Rek, A., et al. 2020. Transition from Childhood to Adulthood in Patients with Duchenne Muscular Dystrophy. *Medicina (Kaunas),* 56.
Wilson, D. G. S., Tinker, A. & Iskratsch, T. 2022. The role of the dystrophin glycoprotein complex in muscle cell mechanotransduction. *Commun Biol,* 5**,** 1022.
Zambon, A. A., Ayyar Gupta, V., Ridout, D., et al. 2022. Peak functional ability and age at loss of ambulation in Duchenne muscular dystrophy. *Dev Med Child Neurol,* 64**,** 979-988.

Appendices
Appendix table of contents

Appendix A. Main characteristics of studies included

EPIDYS (Study 48; NCT02851797)

Table 56: Main characteristics of EPIDYS

Trial name: EPIDYS	**NCT number: NCT02851797**
Objective	To evaluate efficacy and safety of givinostat as an add-on therapy on top of SoC (GCs) in ambulant DMD patients 6 years and older over a period of 72 weeks.
Publications – title, author, journal, year	Mercuri, E., Vilchez, J. J., Boespflug-Tanguy, O., Zaidman, C. M., Mah, J. K., Goemans, N., Müller-Felber, W., Niks, E. H., Schara-Schmidt, U., Bertini, E., Comi, G. P., Mathews, K. D., Servais, L., Vandenborne, K., Johannsen, J., Messina, S., Spinty, S., McAdam, L., Selby, K., Byrne, B., …

Trial name: EPIDYS	NCT number: NCT02851797
	EPIDYS Study Group (2024). Safety and efficacy of givinostat in boys with Duchenne muscular dystrophy (EPIDYS): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet. Neurology, 23(4), 393–403. Mercuri et al. (2024b), Mercuri et al. (2024c)
Study type and design	Multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. EPYDIS was designed as a conventional parallel-group design trial. Since the study was conducted in a paediatric population with a serious and life-threatening disease, the unequal randomisation ratio (i.e., 2:1; givinostat plus GCs and GCs alone) was applied to reduce the exposure to placebo to only one-third of patients and to increase the number of patients who were exposed to givinostat.
Sample size (n)	179
Main inclusion criteria	1: Are an ambulant male aged ≥6 years at randomisation with DMD characteristic clinical symptoms or signs (e.g., proximal muscle weakness, Gowers' maneuver, elevated serum creatinine kinase level) already present at screening 2: Have DMD diagnosis confirmed by genetic testing 3: Are able to complete 2 Four Stairs Climb test (4SC) screening assessments; the results of these tests must be within ±1 second of each other 4: Have the mean of 2 screening 4SC assessments ≤8 seconds 5: Have time to rise from floor between ≥3 and <10 seconds at screening 6: Have manual muscle testing (MMT) of quadriceps at screening Grade ≥- 3 7: Have used systemic corticosteroids for a minimum of 6 months immediately prior to the start of study treatment, with no significant change in corticosteroids type or dosage or dosing regimen (excluding changes related to body weight change) for a minimum of 6 months immediately prior to start of study treatment and a reasonable expectation that dosage and dosing regimen will not change significantly for the duration of the study.
Main exclusion criteria	1: Have exposure to another investigational drug within 3 months prior to the start of study treatment 2: Have exposure to idebenone within 3 months prior to the start of study treatment 3: Have exposure to any dystrophin restoration product (e.g., Ataluren, Exon skipping) within 6 months prior to the start of study treatment

Trial name: EPIDYS	NCT number: NCT02851797
Intervention	Givinostat oral suspension (10 mg/ml), 2 times daily (in a fed state), in combination with standard GC therapy (n=118)
Comparator(s)	Placebo oral suspension (10 mg/ml), 2 times daily (in a fed state), in combination with standard GC therapy (n=61)
Follow-up time	72 weeks
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Primary endpoint** Mean change from baseline in 4 Standard Stairs Climb (4SC) after 18 months of treatment. **Secondary endpoints** • Mean change from baseline in time to rise from floor after 18 months of treatment. • Mean change from baseline in the six-minute walking test (6MWT) after 18 months of treatment. • Mean change from baseline in total North Star Ambulatory Assessment (NSAA) score after 18 months of treatment. • Cumulative loss of function on the NSAA over 18 months. • Mean change from baseline of muscle strength normalized over time after 18 months of treatment. • Mean change from baseline in vastus lateralis muscle fat fraction (VL MFF) at 18 months. • Number of subjects experiencing treatment-emergent adverse events (TEAEs), including serious AEs (SAEs), mild, moderate, and severe TEAEs, from baseline through the end of the study (18 months). • Evaluation of acceptability/palatability of the oral suspension at Week 4, end of study (EOS), and early withdrawal.
Method of analysis	The intention-to-treat population included all randomly assigned boys who received at least one dose of study drug and had at least one non-missing postbaseline four-stair count measure or missing post baseline four-stair count measure due to being either non-ambulatory or otherwise physically unable to take part in the assessment, with treatment group assignment according to initial randomisation. The intention-totreat, group A population (i.e., those with baseline vastus lateralis fat fraction >5% to 30%) was used for the prespecified efficacy analyses; supportive analyses were also done post-hoc in the overall

Trial name: EPIDYS	NCT number: NCT02851797
	intention-to-treat population. The safety population comprised all randomly assigned boys who received at least one dose of study drug, with treatment group assignment defined by the treatment actually received and was used for safety evaluations.
Subgroup analyses	Recruitment was prespecified in two groups: group A consisting of participants with baseline vastus lateralis fat fraction (VLFF) of more than 5% but no more than 30%, and group B consisting of those with a VLFF of 5% or less, or more than 30%. Group A was intended to comprise patients who were not at risk of sudden, complete loss of ambulation but who, if receiving placebo, would show sufficient decline over the study duration in the function, strength, and fat fraction endpoints being tested. These criteria were based on expert opinion (KV), were subsequently published,22–24 and are consistent with the recommendations of a consensus workshop on Duchenne muscular dystrophy outcome measures. Group B was recruited so that the safety of givinostat could be evaluated in a broader population of patients with Duchenne muscular dystrophy.
Other relevant information	

Sources: Italfarmaco (2022a), Mercuri et al. (2024b), Mercuri et al. (2024c)

Analysis sets and definitions

The analysis sets and their definitions are described in Table 57. The Target ITT population (Group A) included all boys with baseline MRS VL MFF >5% to 30%; this population was used for the prespecified efficacy analyses. The Overall ITT population (also referred to as the Safety population) was used for safety evaluations and *post hoc* supportive efficacy analyses. As the efficacy results are consistent between the Overall ITT population and the Target ITT (Group A) population (Mercuri et al. 2024b, Mercuri et al. 2024c), the efficacy results from the Overall ITT population are used to inform the CEM, to use the largest population for which efficacy data are available.

Table 57: EPIDYS | Analysis sets for the Overall ITT and Target ITT population

Analysis set	Definition	Givinostat (n)	Placebo (n)
Overall ITT population (Safety population)	All randomly assigned boys who received ≥1 dose of study drug, and had ≥1 non-missing post-baseline 4SC measure or missing post-baseline 4SC measure due to being either non-ambulatory or otherwise physically unable to take part in the assessment, with treatment group assignment according to initial	118	61

Analysis set	Definition	Givinostat (n)	Placebo (n)
	randomisation; used for safety evaluations and post hoc supportive efficacy analyses		
Target ITT population (Group A)	All boys with baseline MRS VL MFF >5% to 30% (comprised boys not at risk of sudden, complete loss of ambulation, but expected to show decline in the study endpoints over 18 months); used for the prespecified efficacy analyses	81	39
Off-target ITT population (Group B)	MRS VL MFF of ≤5%, or >30%; recruited so that the safety of givinostat could be evaluated in a broader population of boys with DMD	37	22
PK analysis set for the Target population	All boys in the Target ITT population who received ≥1 dose of treatment with givinostat and who had ≥1 post-dose concentration of study drug; used for all formal PK summaries and analyses	80	0
PK analysis set for the Overall population	All boys in Groups A and B who received ≥1 dose of treatment with givinostat and who had ≥1 post-dose concentration of study drug; used for any supportive PK evaluations. Final membership of the PK analysis set in both the Target and Overall populations was confirmed after unblinding	117	0
MRS cohort	All randomly assigned boys in the Target ITT population who completed at least one post-baseline assessment; used for the VL MFF analyses.	77	37

Abbreviations: ITT, intention-to-treat; MFF, muscle fat fraction; MRS, magnetic resonance spectroscopy; n, number; N/A, not applicable; PK, pharmacokinetic; VL, vastus lateralis.
References: Mercuri et al. (2024b), (Mercuri et al. 2024c)}, Italfarmaco (2022a), Italfarmaco (2020)

Statistical methods

Statistical methods used in EPIDYS are summarised in Table 58.

Table 58: EPIDYS | Summary of statistical analyses

Hypothesis objective	**The study hypothesis was that givinostat in addition to SoC improved 4SC by at least 2 seconds compared with placebo in combination with SoC after 18 months of treatment** **The null hypothesis for the primary endpoint was no difference in mean change in 4SC from baseline to 18 months between the givinostat and placebo treatment groups**
Statistical analysis	All analyses done in SAS 9.4 **Primary endpoint statistical analyses** The primary endpoint was analysed using an ANCOVA. As prespecified in the SAP, blinded 4SC data were log-transformed before analysis because they were not normally distributed. The dependent variable was log change in 4SC results

from baseline to 18 months, with log 4SC, time-to-rise, time-to-run or walk 10 metres, and 6MWT as baseline covariates, and randomised treatment, GCs use, and age as independent class variables

Analysis of key secondary endpoints

Key secondary endpoints (change from baseline after 18 months in NSAA total score, NSAA cumulative loss of function, TTRF, 6MWT, knee extension, elbow flexion, and VL MFF) were analysed using a similar ANCOVA (without log transformation), except for NSAA cumulative loss of function, which was analysed using negative binomial regression

Hochberg procedure

The key secondary endpoints were prospectively adjusted for multiplicity using the Hochberg procedure, because they were of equal clinical relevance. In this procedure, p-values are ordered from least to most significant: if the largest one-sided p-value is ≤0.025 then all endpoints are significant; otherwise, the endpoint with the largest p-value is deemed non-significant and the next largest p-value is considered in relation to 0.025/2 = 0.0125. If the nth ordered one-sided p-value reaches ≤0.025/n, treatment effects for that and subsequent endpoints are significant; otherwise, the nth p-value is deemed nonsignificant. As the Hochberg procedure does not account for correlation between endpoints, a *post hoc* permutation test was also done to assess the overall probability of efficacy while accounting for this correlation

Other endpoints

The binary efficacy variables (proportion of boys with >10% persistent worsening in 6MWT, proportion of boys losing ambulation during the study) were analysed using logistic regression. Baseline values for: 4SC, TTRF, time to run/walk 10 metres, distance walked in 6 minutes and re-derived age at first dose (in years and months), were included as independent covariates. Randomised treatment group and concomitant GC use were included as independent classification factors

The time to event variables (time to 10% persistent worsening in 6MWT, time to persistent loss of standing) were analysed using Cox proportional hazards modelling where adjustment of alpha was applied to any of the above analyses, the 2-sided CIs were adjusted as below.

Analysis timepoint	Endpoint	Applicable p-value (1sided)	Applicable p-value (2sided)	CI (2-sided)
Final analysis	4SC at 18 months in the Target ITT population	p≤0.025	p≤0.05	95%

	Key secondary efficacy endpoints at 18 months in the Target ITT population	p≤0.025/i (i=rank according to Hochberg procedure)	p≤0.05/i (i=rank according to Hochberg procedure)	100(1−0.05/i)% (i=rank according to Hochberg procedure)	
General	All other analysis (supportive only)	p≤0.025 (nominal p-values presented)	p≤0.05 (nominal p-values presented)	95%	

Safety data were prespecified to be analysed descriptively only

Sample size, power calculation

Original sample size calculation, and blinded interim futility analysis

The sample size was originally calculated to provide 90% power and a 1-sided alpha of 2.5% to detect a true difference of 3 seconds between givinostat and placebo in the Target ITT (Group A) for 4SC 18 month change from baseline, assuming a common SD of 6 seconds. The estimated SD was based on publicly available Phase 3 study data on ataluren and drisapersen in patients with DMD, in addition to sponsor's data. A pre-planned interim analysis was performed in January 2020 by an independent statistician, after the first 50 boys completed 12 months of treatment. At this interim futility analysis, there was no efficacy assessment, no unblinded analysis of the primary endpoint or early stopping of the study for efficacy and, hence, no alpha spent. The futility analysis was based on MRS VL MFF data at 12 months, with LS means obtained from an ANCOVA model on change from baseline at the respective visit with baseline value and age fitted as covariates, and concomitant GC use and treatment group as independent classification factors. The futility analysis was blinded to the sponsor, and unblinded for the IDMC; the IDMC only communicated to the sponsor whether the study should proceed or be stopped, based on whether the study had met the futility criteria. Futility was considered if the mean change in VL MFF in the givinostat group was equal to or worse (i.e. higher) than that seen in the placebo group. The LS means were 3.61 and 7.95 for givinostat and placebo, respectively, so futility was not met, and the trial continued with a pre-planned blinded sample size re-assessment allowing for a sample size reduction without affecting study power. No other changes to the study conduct were made because of this analysis and there was no bias adjustment

Subsequent sample size calculation

Based on an SD of 3.094 seconds in the masked sample size reassessment (approximately half of that assumed in the original power calculation), 102 boys would provide 90% power, with a one-sided alpha of 2.5%, to detect a difference of 2 seconds in the results of the 4SC between the givinostat and placebo groups at 18 months in the Target ITT (2 second difference confirmed as clinically relevant based on analyses by Wong et al., and substantiated by data from the CINRG natural history database). With an estimated drop-out of 8%, 110 boys were needed in the Target ITT (Group A) and up to 50 (35% of the Overall ITT population) needed for Group B

Data management, patient withdrawals	**Handling of missing data** Any missing values classified as 1 (due to reasons other than being non-ambulatory or physically unable to perform the test/assessment; included missing data due to COVID-19) were imputed using the mean of all non-missing values for the respective measurement and timepoint across all boys randomised to the respective treatment and in the respective concomitant GC stratum and group (i.e. Target ITT or Group B). Any missing values classified as 2 (due to being either non-ambulatory or otherwise physically unable to perform the test/assessment; i.e. disease progression) were imputed by setting the value to 0 or to twice the maximum non-missing value recorded across all boys depending on the directionally of the test. In all cases, imputation of any data classified as 1 were completed first, followed by imputation of any data classified as 2hFor the NSAA assessment, where the total score is a sum of ordinal item scores, for imputation of Class 1 missing data, each item score was imputed using the mode of the non-missing scores for the same item and visit across all boys randomised to the same treatment and in the same concomitant GC stratum and group. If the assessment was attempted and ≤8 were missing, then the missing item scores were imputed using the mode of the non-missing item scores for the boy and visit. If ≥9 items were missing, then the missing item scores for that boy at that visit were imputed as zero. In the event of missing values classified as 2, all item scores and the total score were imputed to zero **Handling of missing data due to patient withdrawals** Missing data at any scheduled timepoint were imputed according to the above rules, including any scheduled timepoints after a boy withdrew early. In these cases, where the final assessment prior to withdrawal was missing and determined to be Class 2 missing data, all missing assessments post withdrawal were also considered Class 2. Otherwise, these were considered Class 1. Where this applied to an NSAA assessment, Class 1 referred to the scenario where 'Was assessment attempted?' = No. Where a date of assessment was required, the predicted date for imputed timepoints post withdrawal was used. The same approach was followed for any completely missing visits prior to withdrawal or completing the study, where no information had been entered into the respective CRF assessment page indicating whether it was performed. Where data entered into the CRF for an assessment were ambiguous such that they do not reflect any of the expected responses outlined above and therefore missing data could not be classified, a worst-case approach was followed and the missing data was assumed Class 2. Cases where data entered into the CRF assessment page which comply with the responses outlined above but additional information was available to contradict the classification were assessed on a case-by-case basis to determine the appropriate classification to be applied
Statistical analysis timepoints	Boys were enrolled between 6 June 2017 and 22 Feb 2022 A pre-planned interim futility analysis was performed on 20 January 2020 as described above. Blinded sample size reassessment followed this analysis Formal analyses were conducted in the Target ITT population for the primary efficacy endpoint and all key secondary efficacy endpoints at 18 months

Abbreviations: 4SC: 4-stair climb; 6MWT: 6-minute walking test; ANCOVA: Analysis of covariance; CI: confidence interval; CINRG: Cooperative International Neuromuscular Research Group; CRF: case report form; DMD: Duchenne muscular dystrophy; IDMC: Independent data monitoring committee; IRT: interactive response technology; ITT: intention-to-treat; LS: least squares; MFF: muscle fat fraction; MR: magnetic resonance; MRI: magnetic resonance imaging; MRS: magnetic resonance spectroscopy; N: number; NSAA: North Star Ambulatory Assessment; PODCI: Paediatric Outcomes Data Collection Instrument; SD: standard deviation; SoC: standard of care; TTRF: time to rise from the floor; VL: vastus lateralis.
Sources: Mercuri et al. (2024b), Mercuri et al. (2024c), Italfarmaco (2022a), Italfarmaco (2022b).

Outcome measures indicative of key disease ambulation milestones in DMD progression

Table 59: Outcome measures indicative of key disease ambulation milestones in DMD progression

Outcome measures	Description	Key findings
Four-stair climb (4SC) (Bendixen et al. 2014, Bushby and Connor 2011, ATS Committee 2002, Duong et al. 2021, McDonald et al. 2010b, McDonald et al. 2013a)	Critical measure of lower limb strength and power, evaluating the time taken for the patient to climb up and down four standard-sized stairs	Predict the loss of the ability to climb stairs over 2 years, the loss of ambulation, and the time to 10% decline in ambulatory capacity A slower 4SC correlated with reduced participation in physical and social activities of daily living and predict loss of stairs-climbing ability and ambulatory capacity Duration of 4SC affects the HRQoL measure PODCI with higher baseline 4SC, leading to greater declines. 4SC is highly correlated with knee extension strength
North Star Ambulatory Assessment (NSAA) (Ricci et al. 2022, Ayyar Gupta et al. 2023, McDonald et al. 2013a, Muntoni et al. 2019, Ricotti et al. 2016)	The NSAA is a key instrument for measuring clinical outcomes in boys and young men with DMD, encompassing tasks like standing, walking, running, climbing stairs, rising from the floor, and lifting objects It is a comprehensive, clinician-rated, and patient-centred 17-item rating scale designed to evaluate the motor abilities of ambulant boys and young men with DMD Each item can be scored as 0 (unable to perform), 1 (modified method but performed goal independently) or 2 (able to perform independently with no obvious modifications)	Total scores on the NSAA range from 0 to 34, with higher scores indicating better ambulatory function and functional performances NSAA total score correlates with the 6MWD and other outcome assessments used in boys and young men with DMD The NSAA score was 13 at 11 years old and decreased to 9 units at 12, with a median age of loss of ambulation of 13 years
Six-minute walking distance (6MWD)	Evaluates the endurance and functional capacity of boys and young men with DMD by	Baseline distance influences the rate of progression of 6MWD.

(Lynn et al. 2015, ATS Committee 2002, Ricci et al. 2022, Arora et al. 2018, Mazzone et al. 2016, Mercuri et al. 2016)	measuring the distance they can walk on a flat, hard surface in 6 minutes, typically measured along a 60-metre level course It is well-established, reproducible, and well-tolerated in ambulatory boys and young men with DMD Challenges relating to 6MWD use include limitations in statistical power owing to cross-patient variability A number of trials have used the 6MWT as a primary endpoint. However, the 6MWT has come under some criticism. TFTs offer potentially appealing alternative primary endpoints for use in ambulatory patients	Data from a study suggested that if the distance walked in 6 minutes was at least 330 metres at baseline, the risk of losing ambulation within two years was significantly reduced For every 30-metre incremental decrease in the baseline 6MWD, the percentage of patients who remained ambulatory over the following two years decreased substantially
Ten-metre walking test (10MWT) (Bushby and Connor 2011, Ricci et al. 2022)	Measures the time it takes to walk/run 10 metres	Completing the task in more than 12 seconds was predictive of loss of ambulation within the next 12 months with a high statistical significance (100%; p< 0.0001) Boys and young men with DMD who could perform the task in less than 6 seconds were significantly more likely to maintain ambulatory ability for longer (100%; p< 0.0001)
Time to rise from the floor (TTRF) (Ricci et al. 2022, Arora et al. 2018, Mazzone et al. 2016, McDonald et al. 2021)	Measures the time in seconds taken to stand up from lying supine on the floor to a straight standing position without help Important indicator of functional mobility and is crucial for understanding a patient's ability to perform daily activities	The mean 12-month 6MWD change was -30.49 metres, -6.23 in those with a baseline TTRF within 7 seconds, and -77.84 in those with more than 7 seconds TTRF declines rapidly over time in boys and young men with DMD and is a prognostic factor of 12-month changes in the 6MWD and for disease progression and loss of ambulation

Abbreviations: 4SC: 4-stair climb; 6MWD: 6-minute walking distance; 6MWT: 6-minute walking test; 10MWT: 10-metre walking test; DMD: Duchenne muscular dystrophy; HRQoL: health-related quality of life; NSAA: North Star Ambulatory Assessment; PODCI: Pediatric Outcomes Data Collection Instrument; TFT: timed function tests; TRF: time to rise from the floor.
Sources: Italfarmaco (2020)

OLE (Study 51; NCT03373968)

Table 60: Main characteristics of OLE

Trial name: OLE (Study 51)	NCT number: NCT03373968
Objective	The primary objective of study 51 was to assess the long-term safety and tolerability of givinostat in DMD patients previously treated in one of the givinostat studies (Study 43 and EPIDYS), and in givinostat-naïve DMD patients (i.e., patients screened in EPIDYS who were eligible for the off-target population but were not randomised in EPIDYS as enrolment in the 'off-target group' was complete)
Publications – title, author, journal, year	Study 51 Clinical Study Report. 5th interim analysis 31 Dec 2023. Version 1.0, 25 June. Italfarmaco. Data on file 2024 Italfarmaco (2024s)
Study type and design	Multi-centre, open-label, long-term, phase II/III study
Sample size (n)	206 (estimated)
Main inclusion criteria	1. Must have participated in one of the previous studies with GIVINOSTAT in DMD and have attended the End of Study Visit or must have been screened in study DSC/14/2357/48 and met: ○ all the inclusion criteria and none of the exclusion criteria, ○ had a baseline vastus lateralis muscle fat fraction (VL MFF) assessed by MRS in the range ≤5% or >30%, i.e. included in "off-target" group, ○ never been randomized because, the enrolment in the off target group was completed. 2. Aged ≥6 years old
Main exclusion criteria	1. Use of any pharmacologic treatment, other than corticosteroids, that might have had an effect on muscle strength or function within 3 months prior to be enrolled in this study (e.g., growth hormone); Vitamin D, calcium, and any other supplements will be allowed; 2. Use of any current investigational drug other than givinostat; 3. Have presence of other clinically significant disease, which, in the Investigator's opinion, could adversely affect the safety of the subject, making it unlikely that the course of treatment or follow-up would be completed, or could impair the assessment of study results;

Trial name: OLE (Study 51)	NCT number: NCT03373968

4. Have a diagnosis of other uncontrolled neurological diseases or presence of relevant uncontrolled somatic disorders that are not related to DMD;
5. Have platelets count, White Blood Cell and Haemoglobin at screening < Lower Limit of Normal (LLN) (for abnormal screening laboratory test results (<LLN), the platelets count, White Blood Cell and Haemoglobin will be repeated once; if the repeat test result is still <LLN, then exclusionary);
6. Have Triglycerides > 300 mg/dL (3.42 mmol/L) in fasting condition at screening visit* (for abnormal screening laboratory test results (>300 mg/dL), the triglycerides will be repeated once; if the repeat test result is still >300 mg/dL, then exclusionary);
7. Have inadequate renal function, as defined by serum Cystatin C >2 x the upper limit of normal (ULN) at screening visit*. If the value is >2 x ULN, the serum Cystatin C will be repeated once; if the repeated test result is still >2 x ULN, the subject should be excluded);
8. Have heart failure (New York Heart Association Class III or IV)
9. Have a current liver disease or impairment, including but not limited to an elevated total bilirubin* (i.e. > 1.5 x ULN), unless secondary to Gilbert disease or pattern consistent with Gilbert's;
10. Have a baseline QTcF >450 msec, (as the mean of 3 consecutive readings 5 minutes apart) or history of additional risk factors for torsades de pointes (e.g., heart failure, hypokalaemia, or family history of long QT syndrome)

Intervention	Givinostat oral suspension (8.86 mg/mL) was administered orally as BID in a fed state. The starting dose of givinostat in Study 51 was at the same level ('A', 'B', or 'C') that the patient was receiving at the end of the previous DMD givinostat study, Study 43 or EPIDYS study. For naïve givinostat DMD patients, the treatment was started with givinostat oral suspension (8.86 mg/mL) as BID dose level 'B', with the dose adjusted by patient weight gain during the trial. For patients coming from Study 43 who received 37.5 mg BID, dose level 'A' was considered, while for those who received 25 mg BID, dose level 'B' was considered. All patients used GCs as per the protocol. There were 176 (85.0%) patients on the deflazacort treatment (161 patients daily and the remaining 15 patients on the intermittent regimen), 34 (16.4%) patients on the prednisone treatment (22 patients daily and 12 patients on an intermittent regimen), and 14 (6.8%) patients on steroids classified under 'other' treatments (9 patients daily and the remaining 5 patients on an intermittent regimen). A total of 12 patients on the prednisone regimen, 20 patients on the deflazacort regimen, and 8 patients on

Trial name: OLE (Study 51)		NCT number: NCT03373968
	other treatment regimens changed to the steroid regimen during the study.	
Comparator(s)	NA	
Follow-up time	Until MA of givinostat	
Is the study used in the health economic model?	Yes	
Primary, secondary and exploratory endpoints	**Primary endpoint** Type, incidence, and severity of treatment-related/not related AEs and serious TEAEs **Secondary endpoints** Ambulant patients: • Physical functions including 6MWT, NSAA, and Time function tests such as TRF, 4SC, 4SC velocity and 10MWT • Muscle strength assessment, focusing on knee extension and elbow flexion, measured by HHM Non-ambulant patients: • Physical function assessment using the EK score • Evaluation of activities of daily living through patient and caregiver reports, measured by Barthel Index All patients: • Physical function as measured by the PUL and MFM • Respiratory function evaluation, including FVC, FEV_1, and PEF • Patient and caregiver QoL assessment, utilizing the PedsQL for paediatric patients and the SF-36 for adult patients Monitoring age-related milestones in the disease progression, including age at loss of ambulation, age at the need for respiratory support during the day, age at scoliosis surgery, and age at death **Exploratory endpoints** • Physical function as measured by the PUL • Mean change of MFM • Respiratory function evaluation, including FVC, FEV_1, and PEF • Monitoring age-related milestones in the disease progression, including age at loss of ambulation, age at the need for respiratory support during the day, age at scoliosis surgery, and age at death Ambulant patients: • Physical functions including 6MWT and NSAA, and Time function tests such as TRF, 4SC and 10MWT	

Trial name: OLE (Study 51)	NCT number: NCT03373968
	• Muscle strength assessment, focusing on knee extension and elbow flexion, measured by HHM Non-ambulant patients: • Mean change in the EK score • Evaluation of activities of daily living through patient and caregiver reports, measured by the Barthel Index Muscle strength assessment, focusing on elbow flexion, measured by HHM **PKs endpoint** Analysis of population PK models to continue assessing givinostat in DMD patients
Method of analysis	All efficacy analyses were performed in the ITT population based on the patients' ambulatory status at baseline. Enrolled patients who had taken at least one dose of therapy and who had at least one post-baseline efficacy assessment were included in the relevant analyses. No hypothesis testing or statistical modelling was carried out for the secondary endpoints. The relevant rules were followed for imputation of missing values. Demography and baseline characteristics were summarized based on the Safety Analysis Set.
Subgroup analyses	All efficacy analyses were performed in the ITT population based on the patients' ambulatory status at baseline. Additionally, analyses were presented by the different treatment groups: givinostat group, delayed givinostat group and givinostat-naïve group (see below). However, the analysis set in the ITT population served as the basis for the formal efficacy analysis. **Givinostat group** A total of 119 patients were enrolled in the givinostat group, of whom eight (6.7%) patients prematurely discontinued the study. Of these, four (3.4%) patients withdrew consent, three (2.5%) patients withdrew because of AEs, and one (0.8%) patient withdrew due to another reason **Delayed givinostat group** A total of 58 patients were enrolled in the delayed givinostat group, of whom seven (12.1%) patients prematurely discontinued the study. Of these, four (6.9%) patients withdrew because of AEs, one (1.7%) patient withdrew because of loss of follow-up, and two (3.4%) patients withdrew due to other reasons **Givinostat group-naïve** A total of 30 patients were enrolled in the givinostat group-naïve, of whom six (10.0%) patients prematurely discontinued the study. Of these, three (10.0%) patients withdrew consent, one (3.3%) patient withdrew because of AEs, one (3.3%) patient withdrew due to loss of follow-up, and one (3.3%) patient withdrew due to another reason

Trial name: OLE (Study 51)	NCT number: NCT03373968
Other relevant information	

Sources: Italfarmaco (2024s)

Analysis sets

The enrolled patients were divided into three treatment groups (Table 61) (Italfarmaco 2024s):

- Givinostat group (n=119): patients who received givinostat in Study 43 or 48
- Delayed givinostat group (n=58): patients who received control in Study 48 and were switched to givinostat in the OLE (Study 51)
- Givinostat-naïve group (n=30): patients who were screened in Study 48 and met all the inclusion criteria and none of the exclusion criteria, and were never randomised because the enrolment in the off-target group was completed

Table 61: Datasets Analysed (All population)

	Givinostat group (N=119)	Delayed givinostat (N=58)	Givinostat-naïve group (N=30)
Enrolled set, n (%)	119 (100.0%)	58 (100.0%)	30 (100.0%)
Safety analysis set, n (%)	119 (100.0%)	58 (100.0%)	30 (100.0%)
ITT set, n (%)	119 (100.0%)	58 (100.0%)	30 (100.0%)
PK analysis set, n (%)	116 (97.5%)	57 (98.3%)	30 (100.0%)

Abbreviations: ITT: intention-to-treat; N: number of patients in the study population; PK: pharmacokinetic
Sources: Italfarmaco (2024s)

Withdrawal from the study

Patient withdrawal from study participation and from the study drug treatment occurred under the following circumstances (Italfarmaco 2024s):

- Withdrawal of consent
- Protocol violation
- Lost to follow-up
- Other reasons at the discretion of the investigator

Patient withdrawal from study in the event of an AE that met the following safety stopping criteria (Italfarmaco 2024s):

- Severe drug-related diarrhoea (≥7 stools per day)
- Any drug-related SAE
- Fridericia-corrected QT interval (QTcF) >500 msec
- Platelet count ≤50 × 10^9/L
- White blood cells ≤2.0 × 10^9/L
- Haemoglobin (Hb) ≤8.0 g/dL
- Study drug treatment was temporality stopped if any of the following occurred (Italfarmaco 2024s):
    - Moderate or severe diarrhoea (>4 stools per day)
    - Platelet count <75 × 10^9/L but >50 × 10^9/L
    - White blood cells <3.0 × 10^9/L but >2.0 × 10^9/L
    - Hb <10.0 g/dL but >8.0 g/dL
    - TG >300 mg/dL (3.42 mmol/L) in fasting condition

The UK Real World Data study

Table 62: Main characteristics of the UK Real World Data study

Trial name: UK real-world data study	**NCT number: NA**
Objective	The aim of the UK real-world data study was to evaluate the effect of continuing GC treatment on pulmonary function in adults with DMD
Publications – title, author, journal, year	Pietrusz, A., Astin, R., Guglieri, M., Desikan, M., Waller, K., Chapman, S., Schiava, M., Brady, S., Soleimani, B., Freebody, J. and Nickol, A 2023. The effect of corticosteroid treatment on pulmonary function in adults with Duchenne muscular dystrophy. Presented at: the 28th International Annual Congress of the World Muscle Society (WMS), Charleston, South Carolina, US., 33, pp.S106-S107. (Pietrusz et al. 2023) Pietrusz, A. 2024. Natural history of DMD cohort attending Neuromuscular Service National Hospital for Neurology and Neurosurgery, Queen Square, London. PowerPoint presentation, Data on file. (Pietrusz 2024)
Study type and design	A multicentre retrospective case note review
Sample size (n)	209
Main inclusion criteria	• Male • Age ≥16 years • Being actively seen as a patient or passed away while under care of the participating centre

Trial name: UK real-world data study	NCT number: NA
	• DMD diagnosis confirmed by mutation analysis in the dystrophin gene or by substantially reduced levels of dystrophin protein (i.e., absent or <5% of normal) on Western blot or immunostaining • Clinical features consistent of typical DMD at diagnosis
Main exclusion criteria	• Female • Age <16 years • Diagnosis of BMC or intermediate dystrophinopathy confirmed by mutation analysis in the dystrophin gene or by presence of dystrophin protein (≥5% of normal) on Western blot or immunostaining • No other exclusion criteria as the aim was to capture the full spectrum of manifestations in the adult DMD population
Intervention	GCs
Comparator(s)	NA
Follow-up time	Data was collected between February 2020 and July 2022
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Primary endpoints** • Loss of ambulation • NIV • FVC
Method of analysis	Not available
Subgroup analyses	Patients were stratified into 3 groups: GC Naïve (taken GCs for 12 months or less), GC stopped (used GCs but stopped prior to transition to adult services) and GC continued (continued GCs into adulthood).
Other relevant information	

Abbreviations: SoC: standard of care; MMT: manual muscle testing, DMD: duchenne muscular dystrophy; 4SC: four stairs climb test; VL MFF: vastus lateralis muscle fat fraction; LLN: lower limit of normal; adverse events: AEs; ITT: intention to treat; EK: Egen Klassification; 6MWT: 6-minute walking test; NSAA: North Star Ambulatory Assessment; TRF: Time to rise from the floor; 10MWT: 10-metre walking test; HHM: Hand-held myometer; PUL: Performance of the Upper Limb; MFM: Motor function measure; FVC: Forced Vital Capacity; Forced expiratory volume in 1 second; PEF: Peak exploratory flow; QoL: quality of life; PedsQL: Pediatric Quality of Life Inventory TM; SF-36: Short Form 36 Health Survey; FEV_1: Forced expiratory volume in 1 second

Sources: Pietrusz et al. (2023), Pietrusz (2024), Pietrusz (2025)

Appendix B. Efficacy results per study

Results per EPIDYS

Table 63: Results per study

Results of EPIDYS (NCT02851797)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
LSM change from baseline: Four-step climb	Givinostat*	81	1.27 (1.17 to 1.37)	NR	NR	NR	0.86	0.75 to 0.99	NR	LS means, CIs, and p-values were obtained from an analysis of covariance model on change from baseline in 4SC at Month 18 with baseline values for: 4SC, time to rise from floor, time to run/walk 10 metres, distance walked in 6 minutes and re-derived age at first dose fitted as covariates, with concomitant steroid use and treatment group as independent classification factors. GLSmean change from baseline should therefore be	(Mercuri et al. 2024d)
	Placebo*	39	1.48 (1.32 to 1.66)								(Mercuri et al. 2024d)

Results of EPIDYS (NCT02851797)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										interpreted as a rate change (EOS/baseline).	
LSM change from baseline: NSAA total score	Givinostat*	81	-2.66 (-3.56 to -1.76)	NR	NR	NR	1.91	0.30 to 3.53	NR	LS means, CIs, and p-values were obtained from an analysis of covariance model on change from baseline total NSAA score at Month 18 with baseline values for total NSAA score, 4SC, time to rise from floor, time to run/walk 10 metres, distance walked in 6 minutes, and rederived age at first dose fitted as covariates, with concomitant steroid use and treatment group as independent classification factors.¤	(Mercuri et al. 2024d)
	Placebo*	39	-4.58 (-5.89 to -3.26)								(Mercuri et al. 2024d)
LSM change from baseline: Cumulativ	Givinostat*	81	3.42 (2.69 to 4.33)	NR	NR	NR	0.61	0.41 to 0.93	NR	At each postbaseline visit, failure to perform each of the 17 items of the NSAA was determined as a score transition from 2 or 1 at baseline to 0 at the respective	(Mercuri et al. 2024d)
	Placebo*	39	5.56 (4.00 to 7.72)								(Mercuri et al. 2024d)

Results of EPIDYS (NCT02851797)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
e loss of function										visit. Cumulative postbaseline items failed was the total number of items failed across all postbaseline visits. Baseline total items failed was the total number of items with a score of 0 at baseline. For subjects who withdraw early, the Early Withdrawal visit itself was excluded from the cumulative count. Subjects were excluded if all items at baseline were scored zero. Estimated cumulative failures, ratio of cumulative failures, CIs, and p-values were obtained from a negative binomial regression on the subject cumulative number of failures across all postbaseline visits. Total failed items at baseline, baseline values for 4SC, time to rise from floor, time to run/walk 10 metres, distance walked in 6 minutes, and rederived age at	

Results of EPIDYS (NCT02851797)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										first dose (in years and months) were included as independent covariates in the model, with randomised treatment group and concomitant steroid use included as independent classification factors. A lower ratio indicates a greater reduction in cumulative loss of function across 18 months for givinostat compared with placebo.	
LSM change from baseline: Time-to-rise, s	Givinostat*	81	9.33 (5.82 to 12.84)	NR	NR	NR	-3.28	-9.57 to 3.02	NR	LS means, CIs, and p-values were obtained from an analysis of covariance model on change from baseline in time to rise from the floor at Month 18 with baseline values for: 4SC, time to rise from floor, time to run/walk 10 metres, distance walked in 6 minutes and re-derived age at first dose fitted as covariates,	(Mercuri et al. 2024d)
	Placebo*	39	12.61 (7.49 to 17.72)								(Mercuri et al. 2024d)

Results of EPIDYS (NCT02851797)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										with concomitant steroid use and treatment group as independent classification factors.	
LSM change from baseline: 6MWT, m	Givinostat*	81	-38.4 (-50.7 to -26.2)	NR	NR	NR	10.0	-12.1 to 32.0	NR	LS means, CIs, and p-values were obtained from an analysis of covariance model on change from baseline in distance walked at the end of the 6MWT at Month 18 with baseline values for: 4SC, time to rise from floor, time to run/walk 10 metres, distance walked in 6 minutes and re-derived age at first dose fitted as covariates, with concomitant steroid use and treatment group as independent classification factors.	(Mercuri et al. 2024d)
	Placebo*	39	-48.4 (-66-3 to 30.5)								(Mercuri et al. 2024d)
LSM change	Givinostat*	81	-0.32 (-0.44 to -0.20)	NR	NR	NR	0.19	-0.03 to 0.40	NR	LS means, CIs, and p-values were obtained from an	(Mercuri et al. 2024d)

Results of EPIDYS (NCT02851797)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
from baseline: Knee extension, N/kg	Placebo*	39	-0.50 (-0.68 to -0.33)							analysis of covariance model on change from baseline in normalised muscle strength at Month 18 with baseline normalised muscle strength and rederived age at first dose fitted as covariates, with concomitant steroid use and treatment group as independent classification factors. If more than 1 measurement was taken at a visit for a subject, the arithmetic mean of the measurements was used.	(Mercuri et al. 2024d)
LSM change from baseline: Elbow flexion, N/kg	Givinostat*	81	-0.10 (-0.17 to -0.03)	NR	NR	NR	0.09	-0.04 to 0.21	NR	LS means, CIs, and p-values were obtained from an analysis of covariance model on change from baseline in normalised muscle strength at Month 18 with baseline normalised muscle strength and rederived age at first dose fitted as covariates, with	(Mercuri et al. 2024d)
	Placebo*	39	-0.19 (-0.29 to -0.09)								(Mercuri et al. 2024d)

Results of EPIDYS (NCT02851797)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										concomitant steroid use and treatment group as independent classification factors. If more than 1 measurement was taken at a visit for a subject, the arithmetic mean of the measurements was used.	
LSM change from baseline: MRS VLFF	Givinostat*	77	7.63 (6.10 to 9.17)	NR	NR	NR	-2.92	-5.64 to -0.20	NR	LS means, Cis, and p-values were obtained from an analysis of covariance model on change from baseline in VL MFF at Month 18 with baseline VL MFF and rederived age at first dose fitted as covariates, with concomitant steroid use and treatment group as independent classification factors.	(Mercuri et al. 2024d)
	Placebo*	37	10.56 (8.33 to 12.78)								(Mercuri et al. 2024d)

Abbreviations: LSM: least-squares mean; MRS; magnetic resonance spectroscopy; NSAA; North Star Ambulatory Assessment; VLFF; vastus lateralis fat fraction

Notes: ¤: Assessed at week 72 in the group A part of the intention-to-treat population. For the MRS VLFF assessment, n=77 for givinostat and n=37 for placebo. The treatment effect estimates and CIs were standardised for presentation on the same scale, with each estimate, upper and lower CI divided by its related SE. The CIs have not been adjusted for multiplicity and should not be used for hypothesis testing. Four-stair climb results were analysed on the log scale and cumulative loss of function was analysed via negative binomial regression. Direction of interpretation has been fixed accordingly.

Sources: Mercuri et al. (2024d)

Additional analyses of EPIDYS Primary Endpoint Change in 4SC

Table 64: Analysis of 4SC, change from baseline at 18 months | Target ITT population

Statistics	Givinostat* (N=81)	Placebo* (N=39)
Log transformation applied		
Number of boys included in analysis, n (%)	81 (100)	39 (100)
GLS mean	1.27	1.48
95% CI for GLS mean	1.17, 1.37	1.32, 1.66
GLS mean ratio (givinostat/placebo)	0.86	
95% CI for GLS mean ratio	0.75, 0.99	
p-value	0.034	
No log transformation applied		
Number of boys included in analysis, n (%)	81 (100)	39 (100)
LS mean	1.25	3.03
95% CI for LS mean	0.31, 2.18	1.67, 4.39
Difference in LS means (givinostat-placebo)	-1.78	
95% CI for difference in LS means	-3.46, -0.11	
p-value	0.037	

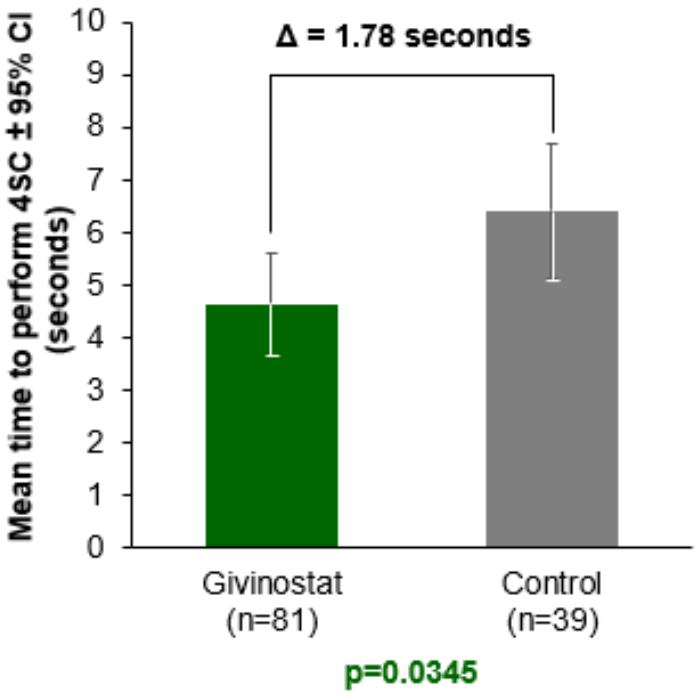
Note: All boys were also receiving systemic GCs, in a dose and regimen that was to remain unchanged over the follow-up period.
Abbreviations: 4SC: 4 stair-climb; CI: confidence interval; EOS: end of study; GLS: generalised least square; ITT: intention-to-treat population; LS: least square; N: number of boys in the study population; n: number of boys meeting the criterion.
References: Mercuri et al. (2024b), Mercuri et al. (2024c)

Non-log-transformed data showed a reduction of ~40% in the decline in 4SC over 18 months for givinostat vs. placebo

As 4SC is a time-based assessment, an analysis of non-log-transformed data was also carried out, to make the outcomes easier to understand. Results of this analysis showed

a treatment effect (change from baseline, givinostat minus control group) of 1.78 seconds, demonstrating a slower statistically significant decline. Using non-log-transformed data at 18 months, mean 4SC changes from baseline were 1.25 seconds (95% CI 0.31 to 2.18) in the givinostat group compared with 3.03 seconds (95% CI 1.67 to 4.39) in the placebo group (LS mean difference –1.78 seconds; 95% CI –3.46 to –0.11; p=0.037; Figure 17 and Table 64 (Mercuri et al. 2024b, Mercuri et al. 2024c). This translates to a reduction of approximately 40% in the decline in the 4SC over a period of 18 months compared with the placebo group. Furthermore, a benefit of 1.78 seconds shorter 4SC adds up considerably across a day to have a large impact across a boy's daily life.

Figure 17: Geometric LS mean change from baseline in time to perform 4SC at 18 months (non-log transformed) | Target ITT population



Note Data are mean (95% CI); the CIs have not been adjusted for multiplicity and should not be used for hypothesis testing; baseline mean values were 3·39 seconds for the givinostat group and 3·48 seconds for the placebo group; *all boys were also receiving SoC, including systemic GCs, in a dose and regimen that was to remain unchanged over the follow-up period
Abbreviations: 4SC: 4-stair climb; CI: confidence interval; LS: least squares; ITT: intention-to-treat, n: number.
References: Mercuri et al. (2024b), Mercuri et al. (2024c)

Improvements in the rate of 4SC decline were consistent when adjusting for changes in the dose of givinostat

Boys received a flexible-dose givinostat regimen, aimed at maximising efficacy, and starting with a high dose that was reduced if treatment was not tolerated. The protocol was amended to lower the starting dose, but the *post hoc* analysis of covariance

(ANCOVA) suggested that the treatment effect was not affected by the change in treatment regimen (Mercuri et al. 2024b, Mercuri et al. 2024c).

The results considering no shift of the 'tipping point' sensitivity analysis to account for missing data for the primary outcome at 18 months were similar to those obtained in the primary 4SC analysis (Mercuri et al. 2024b, Mercuri et al. 2024c).

The company has conducted several additional analyses of EPIDYS data to determine whether dose changes affected the trial results. These confirm that changing the flexible dose regimen during the study did not affect the interpretability of the final study efficacy results and that the givinostat treatment effect was demonstrated independently of the received treatment dose (Italfarmaco 2024a).

Improvements in 4SC with givinostat compared with SoC are clinically meaningful

The significantly smaller decline in 4SC over 18 months with givinostat versus placebo is considered to be clinically meaningful to patients, because slower 4SC correlates with reduced participation in physical and social activities in daily life and predicts loss of stair-climbing ability and ambulatory capacity (Bushby and Connor 2011). A recent publication has shown that 4SC >6.2 seconds is predictive of loss of function in the following year (Arora et al. 2018). At the end of EPIDYS, 12.3% of boys had a 4SC >6.2 seconds in the givinostat group compared with 26.5% in the placebo group. Moreover, the velocity difference between the givinostat and placebo groups of 0.034 tasks per second (Mercuri et al. 2024b, Mercuri et al. 2024c) is similar to the minimal clinically important difference reported by Duong and colleagues (0.035 tasks per second; derived using a questionnaire-anchored approach) (Duong et al. 2021). The effect of givinostat treatment on clinical endpoints versus SoC is explored in the comparative efficacy section (Section 7).

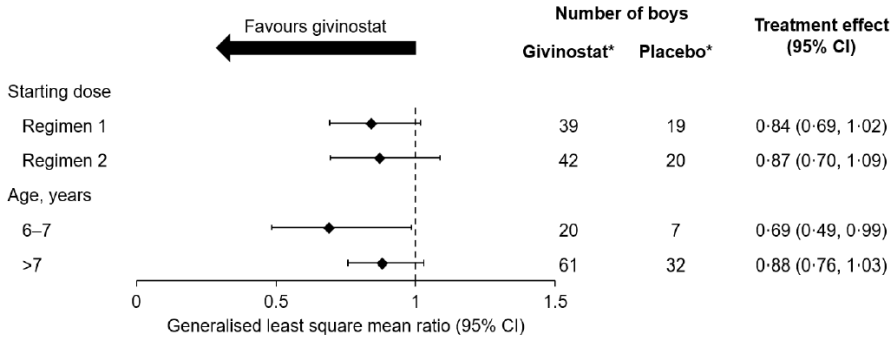
As the treatment effect is at least one-third of the SD of the endpoint (4SC) at baseline, and at least one-third of the SD of the 4SC baselined standard error of measurement, the minimal clinically important difference was demonstrated (Mercuri et al. 2024b, Mercuri et al. 2024c).

EPIDYS Pre-planned subgroup analyses

Subgroup analyses of the EPIDYS primary endpoint showed that responses across treatment groups were consistent for pre-defined subgroups defined by givinostat starting dose and age at first dose (Mercuri et al. 2024b, Mercuri et al. 2024c).

The median total weight-adjusted exposure (mg/kg) in the Overall ITT population was calculated to determine two subgroups: <median or ≥median. For the Target ITT population, the generalised LS mean ratio (givinostat/placebo) was 0.78 seconds for boys in the total weight-adjusted exposure ≥median subgroup for time to 4SC at 18 months for givinostat versus placebo (p=0.0206). The generalised LS mean ratio (givinostat/placebo) was 1.01 seconds for boys in the total weight-adjusted exposure <median subgroup for givinostat versus placebo (p=0.9568) (Italfarmaco 2022a).

Figure 18: Forest plot of subgroup analyses of the primary endpoint (4SC) at 18 months | EPIDYS Target ITT population



Note: Givinostat Regimen 1: weight-based starting dose 20–70 mg bid, with a reduced dose of 13–47 mg bid; Regimen 2: weight-based starting dose 13–47 mg bid, with a reduced dose of 11–37 mg bid. *all boys were also receiving systemic GCs, in a dose and regimen that was to remain unchanged over the follow-up period.
Abbreviations: 4SC: 4-stair climb; CI: confidence interval; ITT: intention-to-treat population.
References: Mercuri et al. (2024b), Mercuri et al. (2024c)

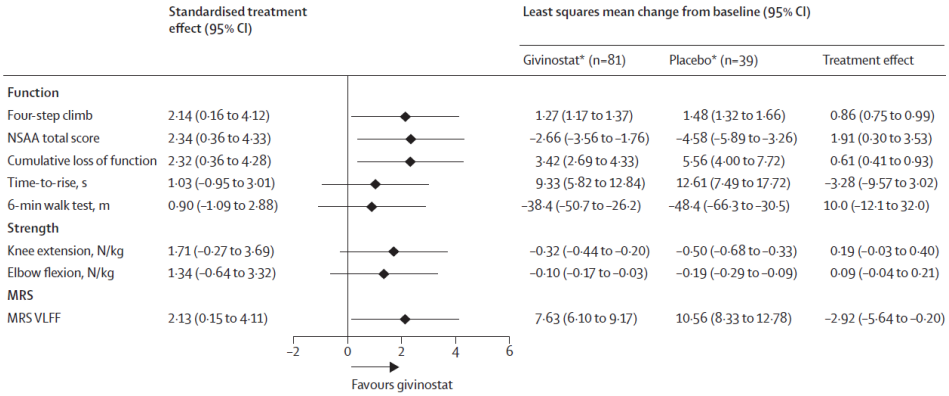
Analyses of EPIDYS Key Secondary endpoints

Secondary outpoint endpoints (i.e. physical function scores, muscle strength scores, and MRS assessment were consistent with the primary 4SC outcome, demonstrating that givinostat impacts the trajectory of the disease and slows muscle mass decline compared with the control group (Mercuri et al. 2024b, Mercuri et al. 2024c).

Given the challenges of powering clinical trials in rare diseases, EPIDYS was designed and powered for the primary endpoint of 4SC. The key secondary endpoints were prospectively adjusted for multiplicity using the Hochberg procedure group (Mercuri et al. 2024b, Mercuri et al. 2024c). After this multiplicity adjustment givinostat was numerically superior to placebo in terms of the decrease in NSAA total score from baseline, cumulative loss of function, and change from baseline in time-to-rise from the floor. The lack of formal statistical significance for the secondary endpoints does not imply an absence of effect; but is indicative of the statistical stringency of the Hochberg adjustment procedure, which does not account for correlations between related endpoints (Mercuri et al. 2024b, Mercuri et al. 2024c).

A *post hoc* permutation test (another statistical approach to account for multiplicity) was done to assess the overall probability of efficacy while accounting for this correlation. This showed that the probability of observing the overall constellation of results under the null hypothesis of no true treatment effect was less than 0.01%, meaning that the positive results seen were highly unlikely to have happened by chance (Mercuri et al. 2024b, Mercuri et al. 2024c).

Figure 19: Forest plot of primary and secondary EPIDYS endpoints at 18 months | Target ITT population



Note: For the MRS VL MFF assessment, n=77 for givinostat and n=37 for placebo; the treatment effect estimates and CIs were standardised for presentation on the same scale, with each estimate, upper and lower CI divided by its related SE; the CIs have not been adjusted for multiplicity and should not be used for hypothesis testing; 4SC results were analysed on the log scale and cumulative loss of function was analysed via negative binomial regression; direction of interpretation has been fixed accordingly
*All boys were also receiving systemic GCs, in a dose and regimen that was to remain unchanged over the follow-up period.
Abbreviations: 4SC: 4-stair climb; CI: confidence interval; ITT: intention-to-treat; MFF: muscle fat fraction; MRS: magnetic resonance spectroscopy; n: number; NSAA: North Star Ambulatory Assessment; SE: standard error; VL: vastus lateralis.
References: Mercuri et al. (2024b), Mercuri et al. (2024c)

An analysis by the Collaborative Trajectory Analysis Project (McDonald et al. 2022a), a loss of 2.0 NSAA items predicted clinically meaningful disease progression, loss of ambulation in the functionally declining group, and loss of ability to rise from the floor in the younger, more stable group. Moreover, complete loss of function in one NSAA item, or deterioration in 1 to 2 items, is perceived as an important change by boys/young men and their parents (Ayyar Gupta et al. 2023). The loss of NSAA items over 18 months in the EPIDYS placebo group confirms that these boys were in a late ambulatory decline phase. The cumulative loss of function was numerically lower with givinostat.

Givinostat treatment was associated with less decline in most of the NSAA items (Figure 22), but particularly on the items that are mostly affected in boys of this age and disease stage (such as the ability to hop and jump) (Mercuri et al. 2023a).

A difference between the givinostat and placebo groups was also observed using muscle imaging, a technique that provides more objective evaluations than the other outcome measures. MRS evidence suggested that there was numerically less fat infiltration in the vastus lateralis at 18 months with givinostat than with placebo (Appendix 0), and the change from baseline was numerically lower in the givinostat group at all timepoints (Figure 25) (Mercuri et al. 2024b, Mercuri et al. 2024c, Vandenborne 2023). Boys in the placebo group had a baseline average VL MFF of 15.45% and an increase of 10.9%, whereas boys treated with givinostat had a baseline average of 15.95% and an increase of 7.5% (Vandenborne 2023). The 30% reduction in VL MFF with givinostat versus placebo at 18 months is predicted to be clinically meaningful, because increased VL MFF inversely correlates with muscle function, daily activity (4SC and TTR) and predicts loss of ambulation (baseline VL MFF value <0.2, functional ability is likely to be preserved,

including ambulation, the ability to climb stairs and rise from the floor, over the subsequent 12 and 24 months; baseline VL MFF >0.3 indicates the likely loss of functional ability over the subsequent 24 months) (Barnard et al. 2020, Nair et al. 2022, Rooney et al. 2020).

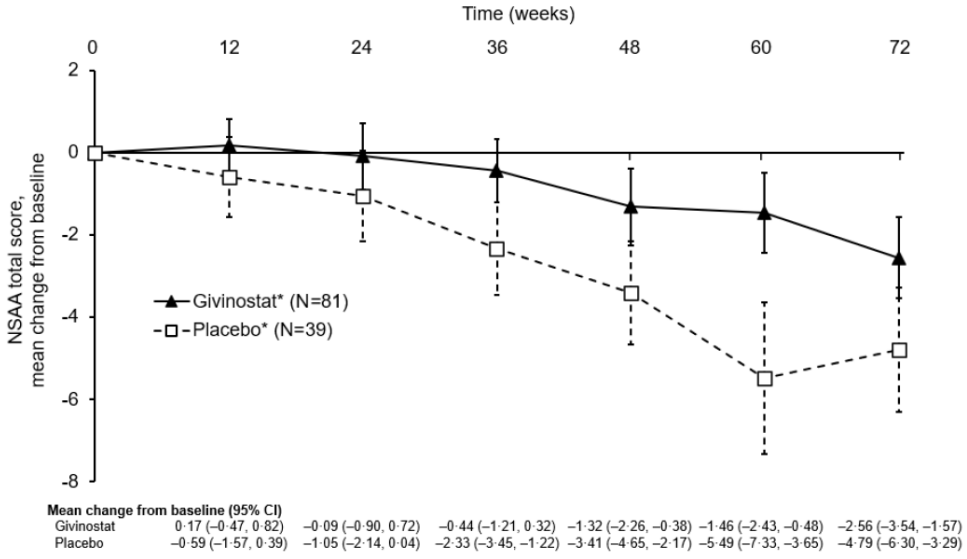
Givinostat reduced fat fraction in four other thigh muscles/muscle groups important for ambulation compared with placebo at 18 months (Vandenborne 2023).

MR biomarkers tend to demonstrate a nonlinear, sigmoidal trajectory over time. There is a strong inverse correlation between VL MFF and measures of clinical function and it is predictive of future ambulatory function and other important clinical milestones. Lower extremity biomarkers predicts functional performance 12 and 24 months later, and the magnitude of change in VL MFF over time is related to the magnitude of change in function (Barnard et al. 2020).

NSAA total score

NSAA is a scale assessing various aspects of functional domains associated with daily activities. The NSAA outcomes in the EPIDYS study mirrored what would be expected from the 4SC primary endpoint results. There was evidence to suggest that decrease in NSAA total score from baseline was numerically lower (i.e. less decline) with givinostat than with placebo, at 18 months (LS mean difference 1.91; 95% CI 0.30 to 3.53; p=0.021; Figure 20) and at all timepoints over the course of the study (Figure 20) (Mercuri et al. 2024b, Mercuri et al. 2024c, Italfarmaco 2022a). (Mercuri et al. 2024b, Mercuri et al. 2024c, Italfarmaco 2022a).

Figure 20: Mean change from baseline over 18 months in NSAA total score | Target ITT population



Note: Data are means and 95% CIs; the CIs have not been adjusted for multiplicity and should not be used for hypothesis testing; baseline mean values were 24.44 and 24.67 for the givinostat and placebo groups,

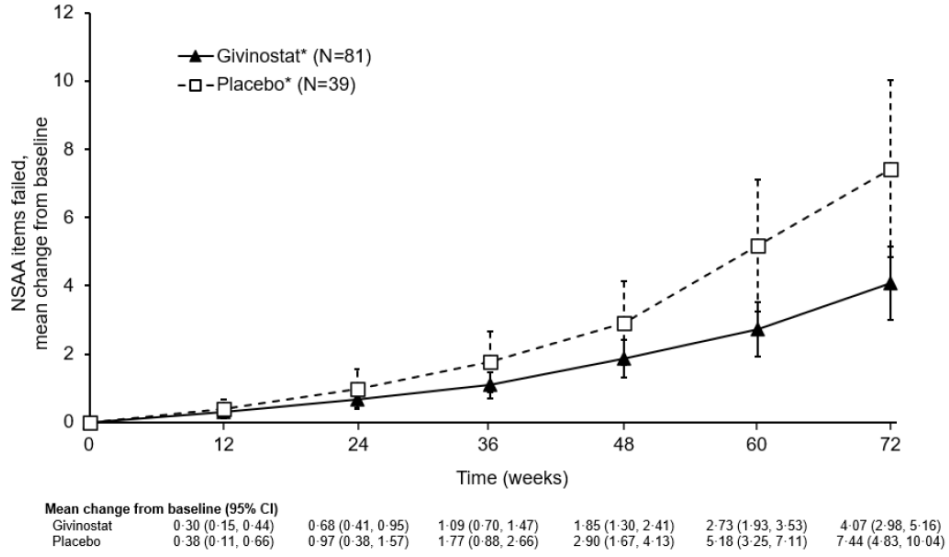
respectively; *all boys were also receiving systemic GCs in a dose and regimen that was to remain unchanged over the follow-up period.
Abbreviations: CI: confidence interval; ITT: intention-to-treat; N: number; NSAA: North Star Ambulatory Assessment.
References: Mercuri et al. (2024b), Mercuri et al. (2024c).

NSAA cumulative loss of function

Cumulative loss of function was also numerically lower with givinostat than with placebo (2.14 fewer items failed over 18 months; 3.42 versus 5.56; ratio 0.61; 95% CI 0.41 to 0.93; p=0.0202), with fewer items failed at each timepoint (Figure 22) (Mercuri et al. 2024b, Mercuri et al. 2024c, Italfarmaco 2022a). This finding is important because in an analysis by the Collaborative Trajectory Analysis Project (McDonald et al. 2022a), a loss of 2.0 NSAA items predicted clinically meaningful disease progression, loss of ambulation in the functionally declining group, and loss of ability to rise from the floor in the younger, more stable group. Moreover, complete loss of function in one NSAA item, or deterioration in 1 to 2 items, is perceived as an important change by boys/young men and their parents (Ayyar Gupta et al. 2023). The loss of NSAA items over 18 months in the EPIDYS placebo group confirms that the boys were in a late ambulatory decline phase.

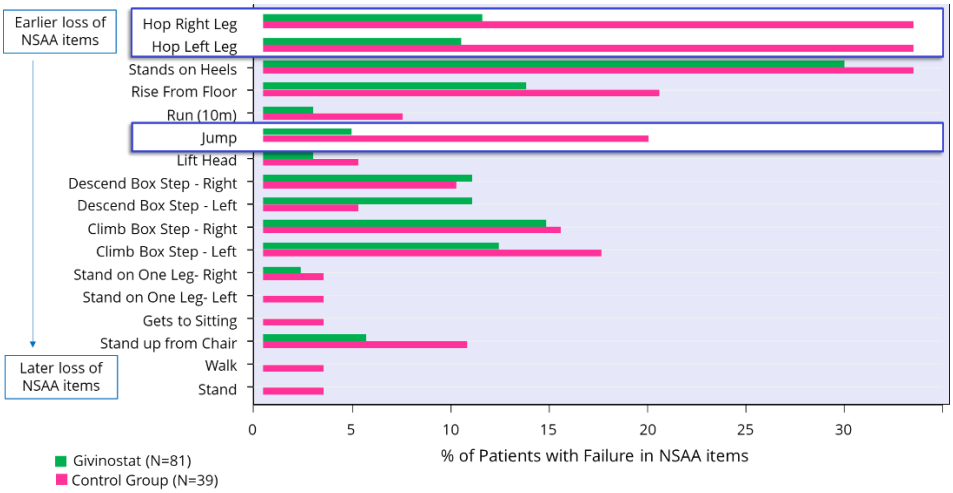
Analysis of the effect on the 17 specific items of the NSAA showed that givinostat treatment was associated with less decline in most of the NSAA items (Figure 22), but particularly on the items that are mostly affected in boys of this age and disease stage (such as the ability to hop and jump) (Mercuri et al. 2023a).

Figure 21: NSAA cumulative loss of function (items failed) over 18 months | Target ITT population



Note: Data are means and 95% CIs; the CIs have not been adjusted for multiplicity and should not be used for hypothesis testing; *all boys were also receiving systemic GCs, in a dose and regimen that was to remain unchanged over the follow-up period.
Abbreviations: CI: confidence interval; ITT: intention-to-treat; N: number; NSAA: North Star Ambulatory Assessment.
References: Mercuri et al. (2024b), Mercuri et al. (2024c)

Figure 22: Loss of NSAA items at Month18 | Target ITT population

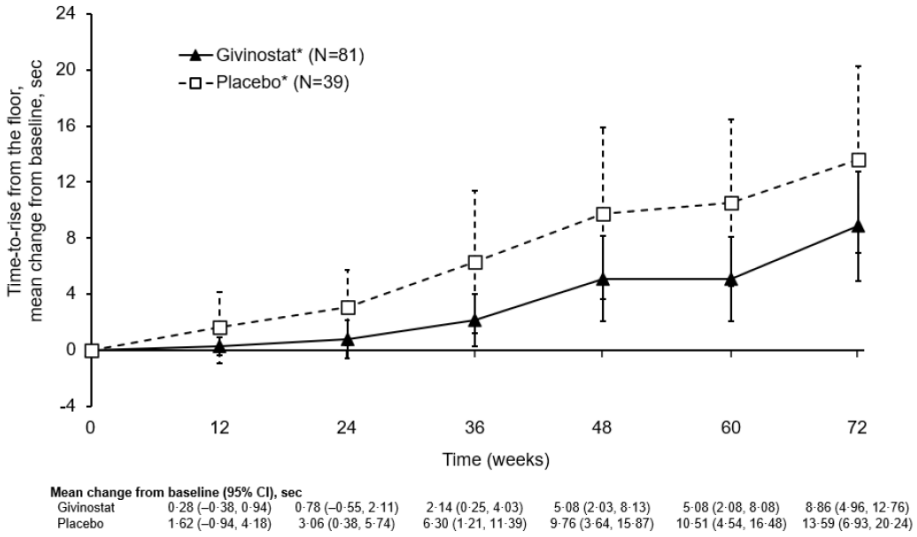


Abbreviations: ITT: intention-to-treat; n: number of boys in the study population; NSAA: North Star Ambulatory Assessment.
References: Mercuri et al. (2023a)

Time to rise from the floor

The change from baseline in TTRF was numerically lower over 18 months with givinostat, with a LS mean difference between groups of –3.28 (95% CI –9.57 to 3.02; p=0.3044; Figure 23), and with a numerically lower mean change from baseline with givinostat at all timepoints (Figure 23) (Mercuri et al. 2024b, Mercuri et al. 2024c, Italfarmaco 2022a).(Mercuri et al. 2024b, Mercuri et al. 2024c, Italfarmaco 2022a). When analysed as velocity (1/time-to-rise), the LS mean difference between givinostat and placebo at 18 months was 0.03 s^{-1} (95% CI 0.007 to 0.055). Large interpatient variability is probably the reason for the non-significant p-value; variability was lower for the analysis of velocity (Mercuri et al. 2024b, Mercuri et al. 2024c). Despite a non-statistically significant difference between the givinostat and placebo group (p=0.3044), these results show a positive trend in boys treated with givinostat and are supportive of the primary endpoint (Mercuri et al. 2024b, Mercuri et al. 2024c, Italfarmaco 2022a).

Figure 23: Mean change from baseline over 18 months in the TTRF | Target ITT population

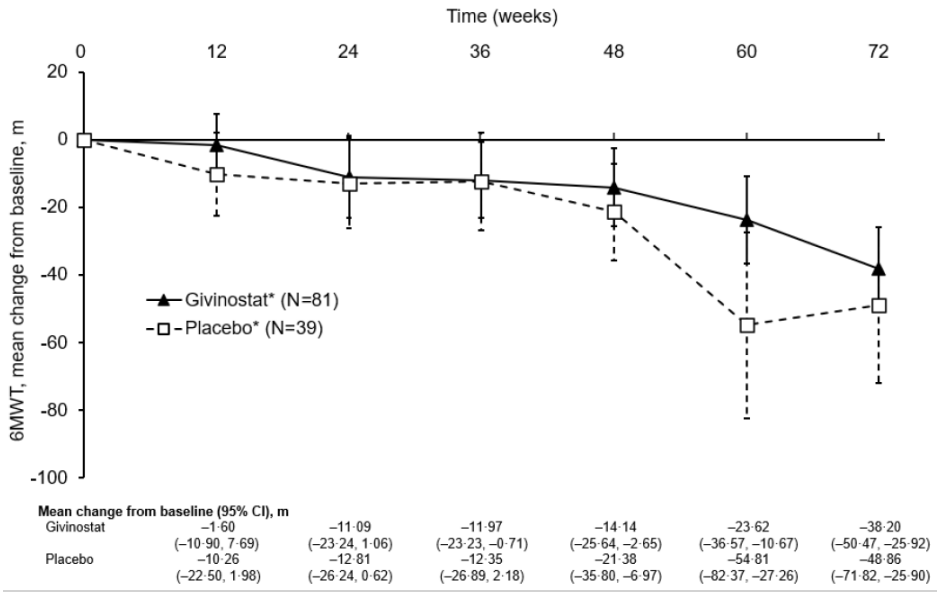


Note: Data are means and 95% CIs; the CIs have not been adjusted for multiplicity and should not be used for hypothesis testing; baseline mean values were 5.57 and 5.59 seconds for the givinostat and placebo groups, respectively; *all boys were also receiving systemic GCs, in a dose and regimen that was to remain unchanged over the follow-up period.
Abbreviations: CI: confidence interval; ITT: intention-to-treat; N: number; TTRF: time to rise from the floor.
References: Mercuri et al. (2024b), Mercuri et al. (2024c)

Distance walked in 6 minutes (6MWT)

The baseline mean 6MWT was 403.3 metres for the givinostat group and 399.6 metres for the placebo group (Mercuri et al. 2024b, Mercuri et al. 2024c). The 6MWT decline over 18 months was slower with givinostat than placebo, with a LS mean difference in distance covered of 10.0 metres (95% CI –12.1 to 32.0; p=0.3723), with lower mean change from baseline with givinostat at all timepoints (Figure 24) (Mercuri et al. 2024b, Mercuri et al. 2024c, Italfarmaco 2022a). The baseline mean in each group was at least 350 metres and boys who can walk these distances are likely to have stable or only slowly declining results for this test, so demonstrating a significant treatment effect would require a much larger sample size (Mercuri et al. 2024b, Mercuri et al. 2024c). Despite the lack of statistically significant difference between the groups (p=0.3723), the results show a positive trend in boys treated with givinostat and are supportive of the primary endpoint (Mercuri et al. 2024b, Mercuri et al. 2024c, Italfarmaco 2022a).

Figure 24: Mean change from baseline over 18 months in the 6MWT | Target ITT population



Note: Data are means and 95% CIs; the CIs have not been adjusted for multiplicity and should not be used for hypothesis testing; baseline mean values were 403.3 and 399.6 metres for the givinostat and placebo groups, respectively; *all boys were also receiving systemic GCs, in a dose and regimen that was to remain unchanged over the follow-up period.
Abbreviations: 6MWT: 6-minute walking test; CI: confidence interval; ITT: intention-to-treat; N, number
References: Mercuri et al. (2024b), Mercuri et al. (2024c)

Muscle strength evaluated by knee extension and elbow flexion

Changes from baseline in knee extension and elbow flexion over 18 months were numerically lower with givinostat than placebo, with LS mean differences between givinostat and placebo of 0.19 N/kg (95% CI –0.03 to 0.40; p=0.0902) for knee extension and of 0.09 N/kg (95% CI –0.04 to 0.21; p=0.1818) for elbow flexion (Table 65) (Italfarmaco 2022a). The changes seen in EPIDYS were small, consistent with a study of the natural history of the disease (Buckon et al. 2016, McDonald et al. 1995).

Table 65: Analysis of muscle strength evaluated by knee extension and elbow flexion normalised by subject weight (N/kg), change from baseline at 18 months | Target ITT population

	Givinostat (N=81)	Placebo (N=39)
Overall knee extension		
Number of boys included in the analysis, n (%)	81 (100)	39 (100)
LS mean	−0.32	−0.50
95% CI for LS mean	−0.44, −0.20	−0.68, −0.33
Difference in LS means (givinostat−placebo)	0.19	

95% CI for difference in LS means	−0.03, 0.40	
P value	0.0902	
Overall elbow flexion		
Number of boys included in the analysis, n (%)	81 (100)	39 (100)
LS mean	−0.10	−0.19
95% CI for LS mean	−0.17, −0.03	−0.29, −0.09
Difference in LS means (givinostat−placebo)	0.09	
95% CI for difference in LS means	−0.04, 0.21	
P value	0.1818	

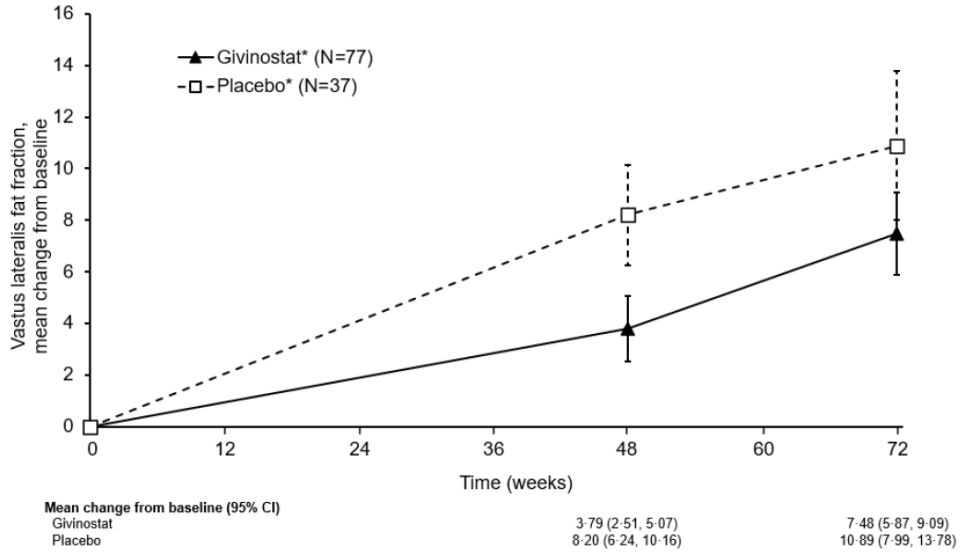
Note: Baseline was defined as the last non-missing value recorded prior to or on the date of first study treatment; LS means, CIs, and p-values were obtained from an analysis of covariance model on change from baseline in normalised muscle strength at Month 18 with baseline normalised muscle strength and rederived age at first dose fitted as covariates, with concomitant GC use and treatment group as independent classification factors; if more than 1 measurement was taken at a visit for a boy, the arithmetic mean of the measurements was used; the overall value was obtained by mean of the respective left and right values.
Abbreviations: CI: confidence interval; ITT: intention-to-treat; LS: least square; N: number in the analysis set; n: number of boys meeting the criterion.
References: Mercuri et al. (2024b), Mercuri et al. (2024c), Italfarmaco (2022a).

Mean change in VL MFF

A difference between the givinostat and placebo groups was also observed using muscle imaging, a technique that provides more objective evaluations than the other outcome measures. MRS evidence suggested that there was numerically less fat infiltration in the vastus lateralis at 18 months with givinostat than with placebo (LS mean difference in fat fraction –2.92; 95% CI –5.64 to –0.20; p=0.0354), and the change from baseline was numerically lower in the givinostat group at all timepoints (Figure 25) (Mercuri et al. 2024b, Mercuri et al. 2024c, Vandenborne 2023). Boys in the placebo group had a baseline average VL MFF of 15.45% and an increase of 10.9%, whereas boys treated with givinostat had a baseline average of 15.95% and an increase of 7.5% (Vandenborne 2023). The 30% reduction in VL MFF with givinostat versus placebo at 18 months is predicted to be clinically meaningful, because increased VL MFF inversely correlates with muscle function, daily activity (4SC and TTRF) and predicts loss of ambulation (baseline VL MFF value <0.2, functional ability is likely to be preserved, including ambulation, the ability to climb stairs and rise from the floor, over the subsequent 12 and 24 months; baseline VL MFF >0.3 indicates the likely loss of functional ability over the subsequent 24 months) (Barnard et al. 2020, Nair et al. 2022, Rooney et al. 2020).

Givinostat reduced fat fraction in four other thigh muscles/muscle groups important for ambulation compared with placebo at 18 months (Vandenborne 2023).

Figure 25: Mean change from baseline over 18 months in VL MFF | Target ITT population



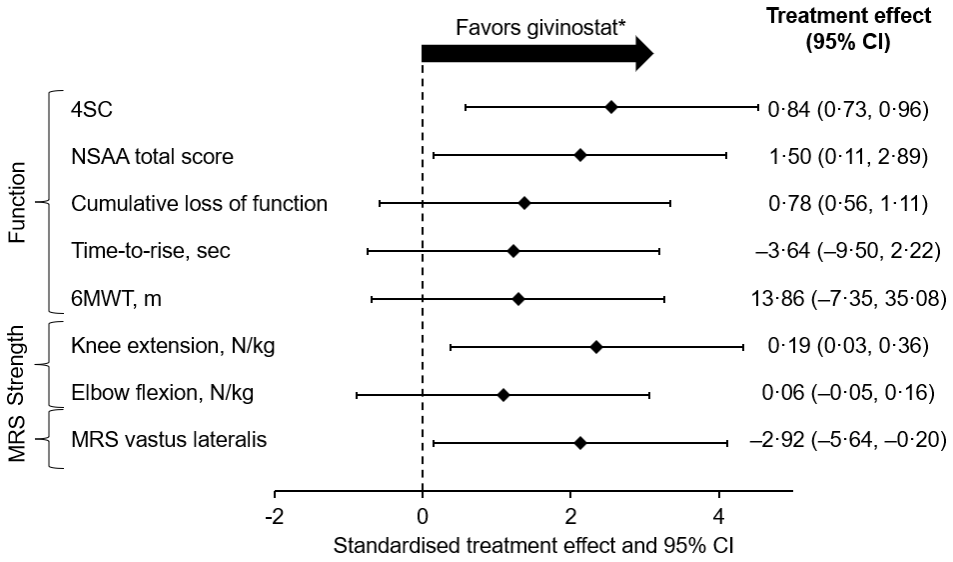
Note: Data are means and 95% CIs; the CIs have not been adjusted for multiplicity and should not be used for hypothesis testing; baseline mean values were 15.45 and 15.95% for the givinostat and placebo groups, respectively; *all boys were also receiving systemic GCs, in a dose and regimen that was to remain unchanged over the follow-up period.
Abbreviations: CI: confidence interval; ITT: intention-to-treat; N: number; VL MFF: vastus lateralis muscle fat fraction.
References: Mercuri et al. (2024b), Mercuri et al. (2024c)

Target ITT population vs. Overall ITT population

A *post hoc* analysis of givinostat efficacy in the Overall ITT population confirmed that the results were consistent with those seen in the Target ITT population (Group A). Supportive analyses were performed to evaluate the effect of givinostat compared with SoC in the Overall ITT population (N=179) on both the primary endpoint (4SC) and six key secondary endpoints (Figure 26) (Mercuri et al. 2024a).

Over the 18-month follow-up period, 4SC decline was significantly slower with givinostat than placebo; generalised least squares (GLS) mean ratio (SD)=0.84 (0.069); p=0.0116 (Mercuri et al. 2024a). Treatment effects relating to the key secondary endpoints consistently favoured givinostat over SoC. Givinostat treatment was associated with less decline in NSAA total score (mean difference: 1.50 points; nominal p=0.035) (Mercuri et al. 2024a).

Figure 26: Forest plot of primary and key secondary endpoints at 18 months | EPIDYS Overall ITT population



Note: Number analysed are 118 for givinostat and 61 for placebo, except MRS vastus lateralis, which is 77 and 37, respectively; plotted treatment effect estimates and CIs were standardised to be presented on the same scale, with each estimate, upper and lower confidence interval divided by its related standard error; 4SC was analysed on the log scale and cumulative loss of function was analysed via negative binomial regression; direction of interpretation has been fixed accordingly; *all boys were also receiving systemic GCs, in a dose and regimen that was to remain unchanged over the follow-up period.
Abbreviations: 4SC: 4-stair climb; 6MWT: 6-minute walking test; MRS: magnetic resonance spectroscopy; NSAA: North Star Ambulatory Assessment.
References: Mercuri et al. (2024b), Mercuri et al. (2024c), Mercuri et al. (2024a)

Results per OLE

PUL and MFM results (Overall population)

For the Overall population (N=207) (December 2023 data-cut), the PUL version 2.0 results showed that the distal-level (wrist and hand dimension score) was stable during the study (Italfarmaco 2024s). For the mid-level (elbow dimension score), there was no decline after one year, there was a mean decline of about 1 point in the second year which was maintained in the third year, and there was a decline of about 2 points from baseline at the fourth year. For the high-level (shoulder dimension score), there was a decline of about 1 point during the first 2 years of treatment, 2 points in the third year and about 3 points from baseline in the fourth year. The mean total score was 38.5 at baseline and changed from baseline by a mean of −1.7 at Month 24, by −3,0 at Month 36 and by −5.2 at Month 48 (Italfarmaco 2024s).

Mean PUL version 1.2 in the first 18 boys until Month 16 was negligibly lower than baseline (Italfarmaco 2024s).

Motor Functions measured with the MFM scale showed slight deterioration during the study, in the total score and in the standing and transfers domain, followed by axial and

proximal motor function domain (Italfarmaco 2024s). The distal motor function scores were quite stable during the study in the Overall population. In this group, the reduction in mean total score at 1 year of treatment was 2.9 points, and was 6.2, 10.6, and 14.1 points at 2, 3, and 4 years of treatment, respectively (Italfarmaco 2024s).

Secondary efficacy analyses in ambulant boys

As expected in a progressive disease, ambulant boys (n=195) showed decline during the study compared with baseline, such that in the fourth year of treatment there was a mean decrease of around 196.3 metres in 6MWT (SD 140.1 metres), 10.7 points mean decline in the NSAA total score, and more time taken for the time function tests (Italfarmaco 2024s). The mean velocity of 4SC decreased by about −0.6 steps per seconds, mean velocity of walk 10 metres by −1.0 m/s, and rise from floor by about −0.1 1/sec (Italfarmaco 2024s). The mean knee extension and elbow flexion muscle strength assessments also showed worsening over time in the Overall population (Italfarmaco 2024s). This is a slower decline than would be expected for a comparative population receiving SoC only.

Additional analyses

The results of an exploratory mixed effect random coefficient analysis suggest that givinostat effects are comparable in boys who were treated with givinostat from the first day in the clinical trial and those whose givinostat treatment was delayed by 18 months (i.e. boys who were received placebo in EPIDYS) (Italfarmaco 2024s). The only notable difference at the Dec 2023 DCO was a difference between the two groups in the annual change for % predicted FVC (which was -4.83 and -2.85 (p=0.02) for the givinostat and delayed givinostat groups, respectively) (Italfarmaco 2024s).

Due to different inclusion/exclusion criteria and givinostat exposure in Study 43 and EPIDYS, an additional *post hoc* analysis was carried out excluding boys from Study 43 (Italfarmaco 2024s). At the Dec 2021 DCO, no significant differences between the givinostat and delayed givinostat groups were noted for all functional and pulmonary parameters. The same results were noted for all physical parameters when the analysis was done excluding the missing values (Italfarmaco 2024s).

Efficacy in young men who became non-ambulant while participating in givinostat studies

The company considers that in view of its mechanism of action, givinostat is expected to counteract muscle deterioration in all muscle types, in all phases of DMD disease, and will continue to be effective after loss of ambulation. However, givinostat has only been studied in patients who are ambulant at treatment initiation. To address question regarding extrapolation of efficacy and safety results from the current givinostat program to non-ambulant patients, the company has conducted a limited assessment of efficacy outcomes in DMD patients who have become non-ambulant while on treatment with either placebo or givinostat in Study 43, EPIDYS or the OLE (Italfarmaco 2024a).

A total of 36 young men have become non-ambulant while participating in givinostat DMD clinical studies (34 patients while receiving givinostat and 2 patients while receiving placebo). The imbalance is due to the difference in the number of boys in the givinostat and placebo groups in the DMD Safety Set and the fact that boys who received placebo in EPIDYS and continued into the OLE were switched to receive givinostat. The small number of young men who became non-ambulant while receiving placebo precludes comparison of givinostat and placebo in this group of patients (Italfarmaco 2024a).

The additional analyses on patients on givinostat who became non-ambulant show a similar trajectory in FVC% before and after loss of ambulation. For FVC%, the estimated difference between the slopes pre- and post-loss of ambulation was −0.173 (95% CI: −0.451, 0.106, p=0.2163) (Italfarmaco 2024a).

Conclusions | EPIDYS and OLE study

In the Phase 3 EPIDYS trial, givinostat significantly slowed the rate of disease progression and showed less decline in muscle function for boys with DMD over 18 months of treatment versus SoC (Mercuri et al. 2024b, Mercuri et al. 2024c). There was a statistically significant and clinically meaningful slowing of decline in the ability to climb four stairs at 18 months for givinostat versus placebo. These changes in muscle function would likely lead to improved participation in physical and social activities of daily life and are predictive of a delay in loss of ambulatory ability.

Secondary endpoint data show that givinostat is likely to provide benefits compared with placebo on other daily living activities important to boys with DMD (such as running, jumping hopping, and rising from a chair) (Mercuri et al. 2024b, Mercuri et al. 2024c). Together these changes in muscle function endpoints indicate a slowing of disease progression, and the potential for a delay in loss of ambulation. Indeed, givinostat showed a slower progression of important endpoints compared with what would be expected in patients receiving SoC.

Longer-term efficacy data from the OLE study support the continued benefit of givinostat treatment. At the fifth interim analysis of the ongoing OLE study, descriptive analyses indicate a slower deterioration of muscle function than would be expected in ambulant boys receiving SoC, but also suggest a delay in the occurrence of major disease milestones, including loss of ambulation (Italfarmaco 2024s). By the December 2023 data-cut, the median age of the loss of ambulation in the givinostat group was 16.7 years, considerably higher than the median age expected in a DMD population treated with GCs only (11 years 8 months in a 2022 analysis of data from the UK North Star Network database) (Zambon et al. 2022), including the Danish DMD population for which LoA occurs at similar age according to a Danish clinical expert (Italfarmaco 2024c). In Norway, for contrast, data show a mean loss of ambulation of 11.1 years (SD: 2.1) in GC-treated boys (Annexstad et al. 2019). Latest data analysis for all the patients in the OLE study receiving givinostat from study entry show median age at loss of ambulation to be 18.1[redacted] years (Italfarmaco 2024s).

In EPIDYS, givinostat provided a statistically significant and clinically meaningful slowing of the decline in ability to climb four stairs compared with placebo (Mercuri et al. 2024b, Mercuri et al. 2024c), indicative of a reduction in the rate of disease progression. The geometric LS mean ratios for the log transformed 4SC results at 18 months versus baseline were 1.27 (95% CI 1.17 to 1.37) in the givinostat group versus 1.48 (95% CI 1.32 to 1.66) in the placebo group (ratio 0.86; 95% CI 0.75 to 0.99, p=0.035) (Mercuri et al. 2024b, Mercuri et al. 2024c). Non-log-transformed data showed a reduction of ~40% in the decline in 4SC over 18 months for givinostat vs. placebo (a 1.78 seconds smaller decline with givinostat) (Mercuri et al. 2024b, Mercuri et al. 2024c). The slower decline in ability to climb four stairs for givinostat compared with placebo is clinically relevant and is expected to lead to improved participation in physical and social activities of daily life, and a prolonged ability to walk.

Boys who received givinostat were also more likely to maintain the ability to do other important activities for longer, including running, jumping, hopping and rising from a chair, compared with those who received placebo (Mercuri et al. 2024b, Mercuri et al. 2024c). Boys with DMD report that they would greatly value being able to walk, run and play sports with their friends and siblings for longer. Cumulative loss of function was numerically lower with givinostat than with placebo (2.14 fewer items failed over 18 months; p=0.0202); this is important because a loss of 2 NSAA items predicts clinically meaningful disease progression and loss of ambulation in a functionally declining group, such as the boys in EPIDYS (McDonald et al. 2022a).

Consistent with the benefits seen on daily activities, muscle strength – evaluated by knee extension or elbow flexion – showed numerically less decline with givinostat than with placebo at 18 months (Mercuri et al. 2024b, Mercuri et al. 2024c) Treatment with givinostat also reduced fat infiltration in thigh muscles by approximately 30% – a benefit which is considered to be clinically meaningful, because increased VL MFF inversely correlates with muscle function, daily activities and predicts loss of ambulation.

Long-term impact for boys and young men with DMD

Longer-term results of the ongoing OLE study support the results from EPIDYS and suggest that givinostat delays the occurrence of major disease milestones, including loss of ambulation. At the December 2023 DCO, 37.7% (n=78) of the Overall population (N=207), had lost ambulation (Italfarmaco 2024s). The median age at loss of ambulation was 16.7 years in the givinostat group and 18.1 (17.3;NE) for all the patients receiving givinostat from study entry, considerably higher than the median age expected in a DMD population treated with GCs only (11 years 8 months in a 2022 analysis of data from the UK North Star Network database) (Zambon et al. 2022) which is similar to DK as mentioned above.

While givinostat does not prevent the major challenges associated with moving from paediatric to adult DMD services, by potentially delaying disease progression, it does mean that this is more likely to occur when boys have better function and abilities (Italfarmaco 2024b).

Givinostat is well tolerated with a predictable safety profile

EPIDYS and OLE study safety results demonstrated a predictable and manageable safety profile for givinostat (Italfarmaco 2024s, Mercuri et al. 2024b, Mercuri et al. 2024c).(Italfarmaco 2024s, Mercuri et al. 2024b, Mercuri et al. 2024c). In EPIDYS, nearly all boys (95%) completed the study, and treatment compliance was high (Mercuri et al. 2024b, Mercuri et al. 2024c). Most AEs observed with givinostat were mild to moderate in severity, they appeared more frequently in the first 3 months of treatment and were generally manageable through dose reduction or interruption (Mercuri et al. 2024b, Mercuri et al. 2024c, Vucinic et al. 2024). No boys died during EPIDYS and no severe or serious AEs were considered related to the study drug or led to withdrawal (Mercuri et al. 2024b, Mercuri et al. 2024c). The most common AEs (diarrhoea, abdominal pain, low platelet levels, and high levels of triglycerides) appear most frequently in the first 3 months of treatment and are generally manageable through dose management (Mercuri et al. 2024b, Mercuri et al. 2024c, Italfarmaco 2024s, Vucinic et al. 2024). Initial results from the small number of boys who became non-ambulant after starting givinostat show no negative effect of the loss of ambulation on givinostat's safety profile (Italfarmaco 2024a)..

Taken together, the primary, key secondary endpoint and AE data from EPIDYS and ongoing OLE study show a grouping of effects that consistently support the long-term efficacy of givinostat in delaying loss of muscle function in boys and young men with DMD (Mercuri et al. 2024b, Mercuri et al. 2024c, Italfarmaco 2024s, Vucinic et al. 2024).

Strengths and limitations of the clinical evidence base

Strengths of the evidence base

Phase 3 EPIDYS outcomes provide confirmatory evidence of givinostat's efficacy, as previously indicated by pre-clinical mouse muscle outcomes and Phase 2 study results (Consalvi et al. 2013, Bettica et al. 2016, Mercuri et al. 2024b, Mercuri et al. 2024c).

- Recruited a broad population of ambulant boys | Compared with those benefitting from mutation-specific antisense therapies, EPIDYS recruited a broad population of boys with DMD, with a wide range of baseline VL MFF values, even within the Target ITT population (Mercuri et al. 2024b, Mercuri et al. 2024c). This population was expected to show sufficient decline with placebo but not to be at risk of a sudden loss of ambulation. The enrichment was effective, with only one boy (receiving placebo) losing ambulation.

- Flexible dosing regimen to maximise efficacy | Boys received a flexible-dose regimen aimed at maximising efficacy, starting with a high dose that was reduced if treatment was not tolerated. The protocol was amended to lower the starting dose, but the *post hoc* ANCOVA suggested that the treatment effect was not affected by the change in treatment regimen.

- Unprecedented Phase 3 randomisation period | The 18-month double-blind study length was chosen to demonstrate a functional benefit of givinostat compared with the SoC only group in the study population (Mercuri et al.

2024b, Mercuri et al. 2024c). By contrast, the treatment period in the Phase 3 ataluren study was 48 weeks (McDonald et al. 2017).

- One of the largest Phase 3 RCTs in DMD | EPIDYS included 179 boys with DMD (Mercuri et al. 2024b, Mercuri et al. 2024c).

EPIDYS included validated, objective and clinically-relevant outcomes and demonstrated clinically meaningful differences versus placebo (both in addition to SoC) (Mercuri et al. 2024b, Mercuri et al. 2024c). The study met its primary endpoint, with significantly smaller decline in 4SC results with givinostat than with placebo in ambulant boys with DMD. No new safety signals were detected, and a high proportion of boys completed the study. The risk of unmasking of study personnel due to permitted dose reductions (mainly in response to AEs) was mitigated by having different people assessing efficacy from those who reviewing safety data. Furthermore, dose adjustments were most often in response to platelet or triglyceride abnormalities, and laboratory results were not communicated to sites until 24 to 48 hours after these efficacy assessments (Mercuri et al. 2024b, Mercuri et al. 2024c).

MRS evidence from EPIDYS added weight to previous histological findings, showing that there was numerically less fat infiltration in the vastus lateralis at 18 months with givinostat than with placebo (Mercuri et al. 2024b, Mercuri et al. 2024c). In a DMD mouse model, givinostat increased cross-sectional myofibre area and decreased inflammatory infiltrate and fibrotic scars (Consalvi et al. 2013), and in Study 43, the drug increased the fraction of muscle tissue and reduced the fraction of fibrosis, necrosis, and fatty replacement in brachial biceps biopsy samples (Bettica et al. 2016). This evidence indicates that givinostat works across both lower and upper limb muscle groups. Overall, the results demonstrate that givinostat positively impacts the trajectory of the disease and preserves muscle mass and function compared with SoC.

The ongoing OLE study is evaluating long-term safety and efficacy, and the full givinostat development programme is gathering additional evidence across the whole DMD treatment paradigm. Results from the ongoing OLE study (Dec 2023 DCO) show that treatment compliance has remained high, and efficacy and safety results that are consistent with those seen in EPIDYS, for boys continuing [redacted] maximum givinostat exposure of up to 10 years) or starting [redacted] givinostat treatment. Median age at loss of ambulation was 18.1[redacted] years (Italfarmaco 2024s), higher than expected in boys and young men with DMD treated with GCs alone (Zambon et al. 2022).

Potential limitations of the evidence base

Only a small number of boys have become non-ambulant after starting givinostat during Study 43, EPIDYS and the ongoing OLE study (Italfarmaco 2024a). The full givinostat clinical development programme will eventually provide evidence from a broad population and in a broad range of patients, including younger boys and those with early disease, boys with all types of genetic mutations, and non-ambulant boys and young men. Givinostat's underlying mechanism of action and preclinical (Consalvi et al. 2013) and clinical results (Bettica et al. 2016, Mercuri et al. 2024b, Mercuri et al. 2024c) to date suggest it is expected to be efficacious regardless of age, disease phase and underlying

DMD mutations. Furthermore, clinical experts consulted by the company have confirmed that there is no clinical rationale for expecting its efficacy to be different in muscles used for walking versus other muscles in the body, such as those involved in hand to mouth function, respiration and cardiac function (Italfarmaco 2024b).

In EPIDYS, almost all boys were white and none of the study centres was in Africa or Asia, although this limitation probably makes the population more generalisable to Denmark (Mercuri et al. 2024b, Mercuri et al. 2024c). Additionally, only males were recruited into the study (Mercuri et al. 2024b, Mercuri et al. 2024c). DMD is an X-linked recessive neuromuscular disorder that predominantly affects males (Birnkrant et al. 2018a); however, further studies are needed to establish the possible effect of givinostat on female carriers, who can manifest the disease in rare cases and often have a very different presentation to males (Quak et al. 2023).

Despite being one of the largest Phase 3 clinical RCTs in DMD, it was not possible to recruit sufficient patients to power all of the key secondary endpoints, due to the rarity of DMD (Mercuri et al. 2024b, Mercuri et al. 2024c). Therefore the finding that EPIDYS secondary endpoints did not reach formal significance after correction for multiplicity was therefore expected; this is especially the case when the commonly applied alpha control mechanisms (which include the Hochberg procedure) do not account for the correlation between the endpoints included (Mercuri et al. 2024b, Mercuri et al. 2024c). However, the results are supported by the *post hoc* permutation test analysis, which showed that the overall constellation of observed positive results were highly unlikely to have happened by chance (Mercuri et al. 2024b, Mercuri et al. 2024c).

Another possible limitation of the study is that due to the protocol amendment (which was conducted without unmasking), some boys started the study on a lower dose of givinostat. This dose reduction did not affect efficacy but did improve overall safety (Mercuri et al. 2024b, Mercuri et al. 2024c), and aligns with practice guidelines recommending similar dose reductions for GCs to manage AEs in DMD (Gloss et al. 2016).

Baseline characteristics of the UK RWD study cohort

Data on types of GD and GC dose (mg/kg) was available for 36 patients, all were in the GC continued group. The mean dose was 0.32 mg/kg (SD: 0.11, range: 0.1-0.57 mg/kg) for prednisolone, and 0.45 mg/kg (SD: 0.15, range: 0.25-0.72 mg/kg) for deflazacort, which is equivalent to 0.38 mg/kg (SD: 0.13, range 0.21 – 0.6 mg/kg) of prednisolone dose (Table 66) (Pietrusz 2025).

Table 66: The UK RWD study cohort stratified by GC type and dose in milligrams per kg

	Total (N=36)

	Prednisolone	Deflazacort	Deflazacort equivalent of prednisolone dose*
Mean (mg/kg)	0.32	0.45	0.38
SD (mg/kg)	0.11	0.15	0.13
Range (mg/kg)	0.1 – 0.57	0.25 – 0.72	0.21 – 0.6

* Deflazacort equivalent of prednisolone dose calculation: step 1: 0.75/0.9 = 5/6; step 2: each deflazacort dose multiplied by 5/6.

Source: Pietrusz (2025)

Data for different GC regimens was available for 132 subjects including 67/132 (50.8%) on daily and 65/132 (49.2%) on an intermittent GC regimen (Table 67). The intermittent regimen was 10 days on, 1 days off apart from a few exceptions including (Pietrusz 2025):

- 10 days on, 20 days off (n=2)
- 30 mg for 10 days, alternated with 12 mg for 10 days (n=1)
- Every other day (n=1)
- 10 days on 5 days off (n=1)

Table 67: The UK RWD study cohort stratified by CS regimen

	Total (N=132)	
	Daily	Intermittent
	49.2% (N=065)	50.8% (n=67)
CS continued	88.1% (N=59)	78.5% (N=51)
CS stopped	11.9% (N=8)	21.5% (N=14)

Source: Pietrusz (2025)

Results of the UK Real-world data study

Results from the retrospective case note are presented in Table 69 below (Pietrusz et al. 2023).

Table 68: Cohort characteristics in the UK real-world data study

	GC naïve	GC stopped	GC continued	Difference
	N=53	N=43	N=113	
AGE at last assessment mean (±SD) [y] range [y]	23.34 (±4.84) 15.92 – 40.5	21.29 (±3.95) 16 – 35.67	21.19 (±2.76) 16.92 – 29.17	p = 0.012

	N=7	N=41	N=102	
CS start AGE mean (±SD) [y] range [y]	8.70 (±1.12) 7.33 – 10.25	7.19 (±1.73) 4 – 11.5	7.20 (±1.96) 4 – 12.42	*p* = 0.231
	N=7	N=43	N/A	
CS stop AGE mean (±SD) [y] range [y]	9.37 (±1.16) 8 – 11	11.70 (±2.51) 8 – 17	N/A	*p* = 0.313
	N=7	N=41	N=102	
CS duration mean (±SD) [y] range [y]	0.67 (±0.35) 0.17 – 1	4.46 (±2.62) 1.33 – 13	14.07 (±2.48) 6 – 21.25	*p* = 0.007
	N=53	N=43	N=113	
Ambulant [%] (N)	0%	0%	4.6%	
AGE at LOA median [y] (IQR) [y]	10 (8.76, 11)	10.67 (9.5, 12.33)	12.67 (10.92, 14)	*p* = <0.001
	N=53	N=43	N=113	
NIV use [%] (N)	81.1% (N=43)	70.5% (N=31)	42.5% (N=48)	
NIV AGE at start median [y] (IQR) [y]	17.33 (15.33, 20)	16 (13.67, 19.67)	19.17 (17.63, 22.34)	*p* = 0.0031
	N=43	N=31	N=48	
LOA to NIV start median [y] (IQR) [y]	7.5 (5.08, 9.83)	5.67 (4.08, 8.75)	7.58 (5.5, 9.54)	*p* = 0.2161
FVC <1L median [y] (IQR) [y]	20.5 (17.21, 22.84)	19.25 (16.71, NA)	24.75 (23.88, NA)	*p* = <0.0001
FVC%p <60% median [y] (IQR) [y]	16.08 (16, NA)	16 (16, 18.09)	16.17 (16, 18.375)	*p* = 0.0222
FVC%p <50% median [y] (IQR) [y]	16.75 (16.17, 17.29)	16.25 (16, 17.88)	17.5 (16.08, 20.64)	*p* = 0.0031
FVC%p <30% median [y] (IQR) [y]	18.38 (17.29, 22.96)	17.04 (16.59, NA)	22.79 (19.54, NA)	*p* = <0.0001
	N=174			
	N=51	N=38	N=85	
Scoliosis (%) (N)	94.1 % N=48	92.1% N=35	65.9% N=56	
	N=146			
	N=48	N=35	N=63	
Scoliosis surgery (%) (N)	58.3% N=28	51.4% N=18	30.2% N=19	

Abbreviations: GC: glucocorticosteroid; LOA: loss of ambulation; NIV: non-invasive ventilation; FVC: forced vital capacity; FVC%p: forced vital capacity percent predicted for age.

Reference: Pietrusz et al. (2023)

The results from the UK real-world data study suggest that early cessation of GC therapy may lead to a loss of steroid effect as evidenced by:

- Lower median age at NIV start compared to GC naïve and GC continued groups

- Shorter period between NIV start and loss of ambulation despite delayed loss of ambulation in GC stopped group
- Younger age att FVC<1L and FVC%p <60%, <50%, and <30%
- FVC and FVC%p longitudinal trajectories throughout adulthood similar to the GC naïve group

Appendix C. Comparative analysis of efficacy

Table 69: Comparative analysis of studies comparing givinostat to SoC for patients with DMD

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
Age at LoA	EPIDYS OLE UK RWD	NA	NA	NA	Unadjusted			Unanchored MAIC. Details of methodology described in Appendix **Error! Reference source not found.**	Yes
					0.222	0.153, 0.323			
					Weighted (Robust SE)				
					0.185	0.121, 0.282			
					Weighted (Bootstrap)				
					[redacted]	[redacted]			

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
Age at NIV	EPIDYS OLE UK RWD	NA	NA	NA	Unadjusted			Unanchored MAIC. Details of methodology described in Appendix **Error! Reference source not found.**	Yes
					[redacted]	[redacted] [redacted]			
					Weighted (Robust SE)				
					[redacted]	[redacted] [redacted]			
					Weighted (Bootstrap)				
					[redacted]	[redacted]	[redacted]		
Age at FVC <1L	EPIDYS OLE UK RWD	NA	NA	NA	Unadjusted			Unanchored MAIC. Details of methodology described in Appendix **Error! Reference source not found.**	Yes
					[redacted]	[redacted] [redacted]			
					Weighted (Robust SE)				

Outcome	Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
					[redacted]	[redacted]			
					Weighted (Bootstrap)				
					[redacted]	[redacted]			

Note: Bold text indicates a significant difference between treatments.
Abbreviations: 1L: 1 litre; CI: confidence interval; DMD: Duchenne Muscular Dystrophy; ESS: effective sample size; FVC: forced vital capacity; HR: hazard ratio; MAIC: matching-adjusted indirect comparison; NE: not evaluable; SE: standard error, SoC: Standard of care.

Summary of studies included in the indirect treatment comparison

Two primary evidence sources inform the ITC analyses for givinostat, EPIDYS and the OLE study. Patients in the two givinostat studies were eligible to be included in the ITC if they had received givinostat from study entry, i.e. patients who were randomised to placebo in EPIDYS and who received delayed givinostat in the OLE study were excluded given the treatment effect in those patients will be confounded. Patients enrolled in EPIDYS who went on to enrol in the OLE study were assessed based on their most recent follow-up to avoid double counting. Patients who were enrolled in the OLE (Study 51) but were previously enrolled in Study 43 were excluded due to different inclusion/exclusion criteria and givinostat exposure in Study 43 and EPIDYS.

The identified UK real-world data source is the most appropriate data source to use to estimate the efficacy of patients receiving SoC, as this reflects both the UK DMD population and UK clinical practice (Pietrusz et al. 2023, Pietrusz 2024). Nordic clinical experts have confirmed that they all follow the same international guidelines and that the UK data is relevant to the Nordic setting in terms of SoC, and disease milestones (Italfarmaco 2024c, Italfarmaco 2024d, Italfarmaco 2024f). A sensitivity analysis compares givinostat with SoC using international data from the CINRG Duchenne Natural History Study (DNHS), excluding patients who were naïve to GC treatment or had received investigational drugs for DMD in previous clinical trials (Henricson et al. 2013, Mercuri et al. 2023b). The published CINRG data used in the sensitivity analysis is not as recent as the UK real-world data and contain overestimations of some of the disease milestones (NICE 2023a, Mercuri et al. 2023b, McDonald et al. 2013b) which was also confirmed by expert in the field in Denmark (Italfarmaco 2024c). Therefore, it was not considered for the base case ITC analyses.

The UK real-world data reflects a multicentre, retrospective case note review study including 209 patients who were treated at University College London, the Newcastle upon Tyne or Oxford university hospitals. Patients were stratified into three groups: GCs naïve (taken GCs for 12 months or less; n=53); GCs stopped (used GCs for at least 12 months but stopped prior to transition to adult services; n=43); and GCs continued (continued GCs into adulthood; n=113).

Table 70 summarises the study design of EPIDYS, the OLE study and the UK real-world data. In total, 148 patients receiving givinostat were included in the ITC: 102 patients were enrolled in both EPIDYS and the OLE study; 16 patients were enrolled in EPIDYS only and 30 patients were receiving givinostat for the first time in the OLE study. For patients receiving SoC, 156 patients were included in the ITC, 113 of whom received continuous GCs, and 43 patients had stopped GC treatment prior to transitioning to adult services. Patients who received GCs for <12 months were not included in the analysis as this group are not reflective of Danish clinical practice (Italfarmaco 2024f).

Table 70: Study design of the studies included in the indirect treatment comparison

Study	Treatment intervention	N	Phase/ blinding	Centre	Study design	Sample size for ITC
EPIDYS (Study 48) (NCT02851797)	Givinostat	118	Phase 3, double-blind	Multicentre	RCT	118 patients: • 102 patients were also enrolled in OLE study • 16 patients unique to EPIDYS
	Placebo	61				N/A
OLE study (Study 51)† (NCT03373968)	Givinostat	110	Long-term study, open-label	Multicentre	Enrolling patients who have been previously treated in previous givinostat studies or who met all inclusion/ exclusion criteria for EPIDYS, but had baseline MRS VLFF in range ≤5% or >30%	132 patients: • 102 patients previously treated with givinostat in EPIDYS • 30 patients who were givinostat naïve at study start‡
	Delayed givinostat	54				
	Naïve givinostat‡	30				
UK real-world data	GCs stopped prior to transition to adult services	43	N/A	London, Newcastle and Oxford	Retrospective case note review	156 patients receiving standard of care
	GCs continued to adulthood	113				
	GCs naïve	53				N/A

Note: †Dec 2023 DCO; ‡Met all the inclusion criteria and none of the exclusion criteria for EPIDYS, and not randomised as enrolment in the "off-target" group was completed, subjects received givinostat for the first time in the OLE study.

Abbreviations: DCO: data cut off; ITC: indirect treatment comparison; MRS VLFF: magnetic resonance spectroscopy vastus lateralis fat fraction; N/A: not applicable, NR: not reported; OLE: open-label extension; SoC: standard of care; UK: United Kingdom.

Baseline characteristics

Baseline characteristics for each of the patient groups included in the ITC by study and pooled are reported in Section 6.1.2.1. There was minimal availability of baseline characteristics in the UK real-world data; only GCs start age was reported. The UK real-world data patients (pooled GCs stopped and GCs continued) started GCs at an older age (7.20 years) compared with pooled EPIDYS and the OLE study (6.09 years). Due to the real-world evidence nature of the data set, it is unknown how comparable other characteristics were across the datasets. However, the UK real-world data represent a clinically relevant population who would be eligible to receive givinostat in Denmark.

Outcome availability

Table 71 shows the outcome measure availability for the studies included in the ITC. The UK real-world data reported both Kaplan-Meier (KM) curves and medians for age at non-invasive ventilation (NIV), time to predicted forced vital capacity (pFVC) <30%[3], age at forced vital capacity (FVC) <1L and overall survival (OS). In addition, medians were reported for age at loss of ambulation, age at pFVC <60%, age at pFVC <50% and age at pFVC <60%.

The EPIDYS and the OLE studies collected the same endpoints as the UK real-world data, as well as additional endpoints including age at loss of 4SC and age at loss of rise from floor; however, for age at NIV, subsequent non-ambulatory health states and overall survival the data are immature with no events observed due to the trial planned study period ending. Therefore, alternative methods were required to estimate the KM curves for these outcomes at later follow-ups to enable an ITC to be conducted. Additionally, where the UK real-world data only reports a median, alternative methods were required to estimate the KM to allow a more robust ITC to be conducted.

Table 71: Outcome availability for the studies included in the indirect treatment comparison

Outcome	Pooled EPIDYS/OLE		UK real-world data		
	Givinostat group		Standard of care		
	Reported	Note	Reported	Median reported	KM reported
Age at loss of ambulation	Y	-	Y	Y	N
Age at loss of 4SC	Y	-	N	N	N
Age at loss of rise from floor	Y	-	N	N	N
Age at NIV	Y		Y	Y	Y

Outcome	Pooled EPIDYS/OLE		UK real-world data		
	Givinostat group		Standard of care		
	Reported	Note	Reported	Median reported	KM reported
Age at pFVC <50%	Y	No events available for analysis†	Y	Y	N
Age at pFVC <30%	Y		Y	Y	N
Age at FVC <1L	Y		Y	Y	Y
Additional outcomes available, but not of interest for ITC and CEM					
Age at pFVC <60%	Y	No events available for analysis†	Y	Y	N
Time to pFVC <30%	Y		Y	Y	Y
OS	Y		Y	Y	Y

Notes: [1] Note this was not reported as *age at* time to pFVC <30%; †Zero events were reported for age at first occurrence of respiratory support in the OLE study. [1] Note this was not reported as *age at* time to pFVC <30
Abbreviations: 1L: 1 litre; 4SC: 4-stair climb; FVC: forced vital capacity; IPD: individual patient data; ITC: indirect treatment comparison; KM: Kaplan-Meier; LOA: loss of ambulation; NIV: non-invasive ventilation; pFVC: predicted forced vital capacity.

Matching-adjusted indirect comparison (MAIC)

From the included studies, individual patient data (IPD) were available for patients receiving givinostat whilst aggregate-level data were available for those receiving SoC. One methodology that can be used to derive the relative efficacy of givinostat versus SoC when IPD for all trials are not available, are MAICs. The MAICs are unanchored as there is no common comparator to link givinostat with SoC beyond the initial follow-up period of 18 months reported for the EPIDYS trial. The MAIC methods used are in line with the published guidance in NICE Decision Support Unit (DSU) Technical Support Document (TSD) 18, and Phillippo 2018 (Phillippo D 2016, Phillippo et al. 2018).

The MAIC approach adjusted for baseline differences in potential prognostic factors and treatment effect modifiers by re-weighting the available IPD for givinostat to match the average baseline characteristics of the SoC treatment group, for which only aggregate data are reported. MAIC is a non-parametric likelihood reweighting method that allows a propensity score logistic regression model to be estimated with the potential prognostic factors and treatment effect modifiers as predictors in the model. Re-weighting the IPD through MAIC methods in this way can reduce (or remove) observed imbalances in patient characteristics between two treatments. Outcomes for each treatment can then be compared between the balanced trial populations. To account for the fact that weights are estimated rather than fixed and known, standard errors (SE) for the MAIC estimates were calculated using both a robust sandwich variance estimator and a bootstrap estimator as per recommendations in the NICE DSU TSD 18 guidance (Phillippo D 2016) and in alignment with DMC recommendations (Medicinrådet 2025a).

Age at start of GC therapy was available from the UK real-world data and this was included as a matching variable in the MAIC. Where there was a published KM curve for a specific outcome, the proportion event-free was extracted using Engauge Digitizer 12.1, and pseudo-IPD was reconstructed using the algorithm published by Guyot et al. (2012).

Acceleration factor

As presented in Table 71 in Appendix C, a limitation with the data available is the lack of reported KM data for loss of ambulation for the UK real-world data and the immature data available for non-ambulatory outcomes for givinostat. Therefore, acceleration factors were utilised to enable comparison from the available data, in addition to make a population-adjustment via the MAIC.

Loss of ambulation

Although it is possible to conduct time-to-event ITCs using median survival estimates to calculate a hazard ratio (HR) for the comparison between two treatments (Tierney et al. 2007), this approach assumes that the hazard of experiencing an event is constant over time. This assumption is clearly violated if outcomes are modelled from birth and patients do not experience loss of ambulation until a few years after birth. Additionally, for loss of ambulation, the median is only reached for the givinostat dataset at the end of the KM curve where there are very few patients still at risk (median survival for givinostat was not reached post-weighting in the MAIC, making the HR from medians not estimable). Given these limitations, it was not deemed appropriate to directly compare the medians between the treatment arms.

Therefore, an alternative approach was considered to generate a KM curve for age at loss of ambulation for SoC, which involved the following steps using the published UK real-world data:

- The KM curves for the age at NIV were digitised for both the GCs stopped and continued groups
- Acceleration factors were derived between age at loss of ambulation and age at NIV, by dividing the median age at loss of ambulation and median age at NIV for the GCs stopped and continued groups
- The derived acceleration factors were applied to the digitised age at NIV KM data to provide estimated age at loss of ambulation. By applying an acceleration factor the analysis assumes that the shape of the KM curve between the outcomes is the same but loss of ambulation events occur at a multiple of time earlier
- Note, given that loss of ambulation is expected to occur prior to a patient receiving NIV, it was considered conservative not to re-censor patients.

Utilising this approach generates a KM curve which is a broadly similar shape to the CINRG DNHS loss of ambulation KM curve (see Figure 27 in Appendix C) although patients in the UK real-world data are typically estimated to experience loss of

ambulation at a slightly younger age which is in line with the reported median age at loss of ambulation in the two studies (UK real-world data [GCs stopped; n = 43]: 10.67 years [10.31, 11.55]; UK real-world data [GCs continued; n = 113]: 12.67 [12.37, 13.45]; CINRG [n=261]: 13.0 [12.0, 14.0]).

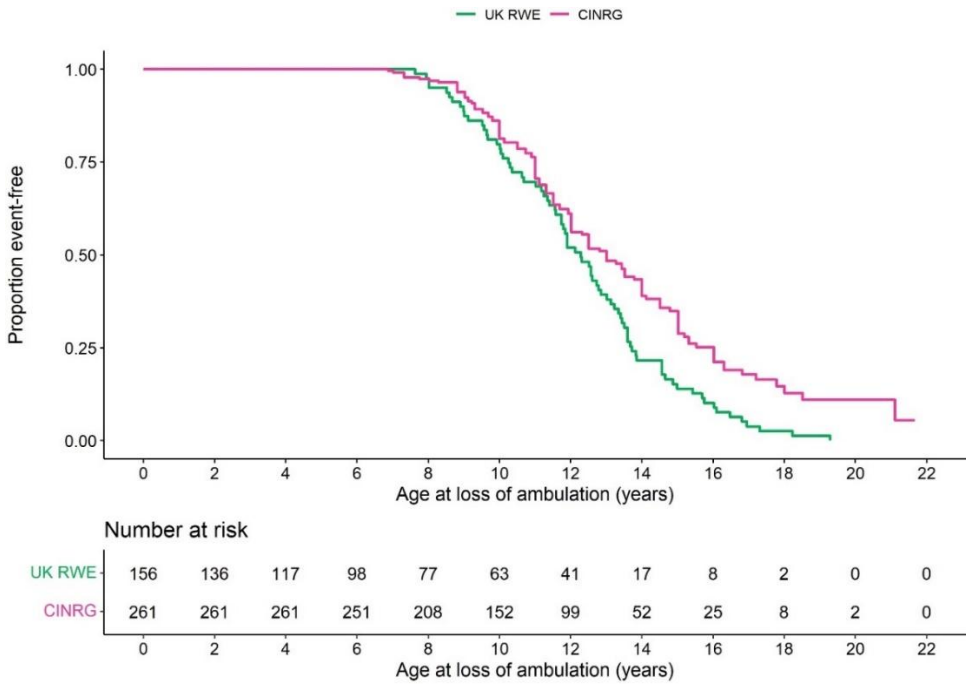
Non ambulatory patients

As the lung function outcomes for givinostat are immature, with zero events occurring during the study follow-up period for respiratory support (Figure 28 in Appendix C), it is not possible to form a direct comparison with SoC nor to extrapolate the givinostat KM data for these outcomes. Consequently, an alternative approach was used to estimate the KM data for the non-ambulatory outcomes for givinostat.

- Using both the estimated median age at loss of ambulation and the median age at each available respiratory outcome from the UK real-world data, an acceleration factor was derived between age at loss of ambulation and age at the respiratory outcome
- The acceleration factor was then applied to the givinostat age at loss of ambulation data to provide an estimated age for each of the non-ambulatory outcomes.

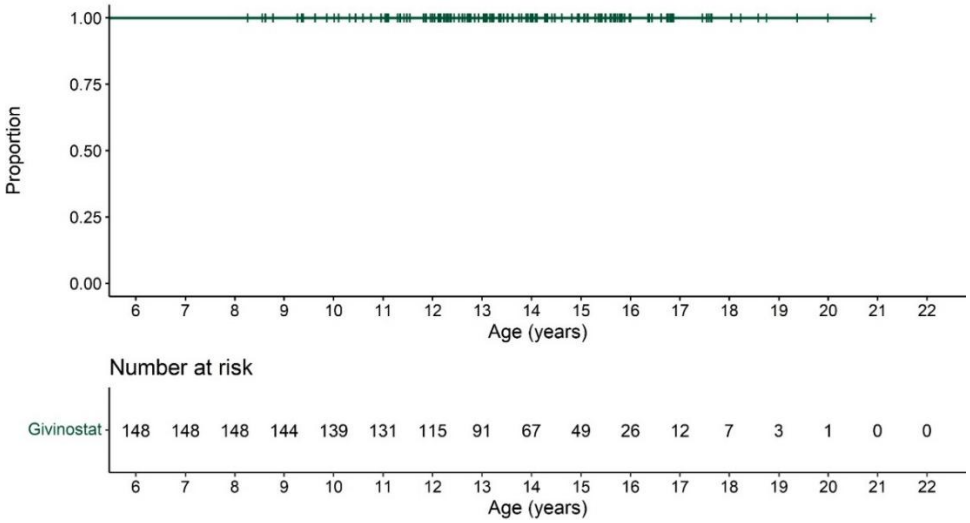
This approach assumes that the relationship between the age at loss of ambulation and the age respiratory outcomes is the same for both givinostat and SoC. Humbertclaude et al. 2012 found that age at loss of ambulation is predictive of both the age at which the peak FVC is realised, and the absolute peak obtained FVC (Humbertclaude et al. 2012). These findings are supported by McDonald et al. 2018b who demonstrate age at loss of ambulation predicts time to an absolute FVC of 1 L and Levine et al. 2023 who show that the decline in percentile predicted FVC and total lung capacity correlate with age and loss of ambulation (McDonald et al. 2018, Levine et al. 2023). Therefore, it is expected that the improved skeletal muscle integrity/ function achieved through treatment with givinostat compared to SoC, as demonstrated through the earlier outcomes observed in EPIDYS and the OLE study, will translate to improved longer term outcomes – regardless of whether a patient remains on treatment with givinostat.

Figure 27: Comparison of acceleration factor estimated UK real-world data loss of ambulation Kaplan-Meier curve with the observed CINRG DNHS loss of ambulation Kaplan-Meier curve



Abbreviations: CINRG DNHS: Cooperative International Neuromuscular Research Group Duchenne Natural History Study; KM: Kaplan-Meier; UK: United Kingdom.

Figure 28: KM plot of age at first occurrence of respiratory support | givinostat (EPIDYS and OLE study)



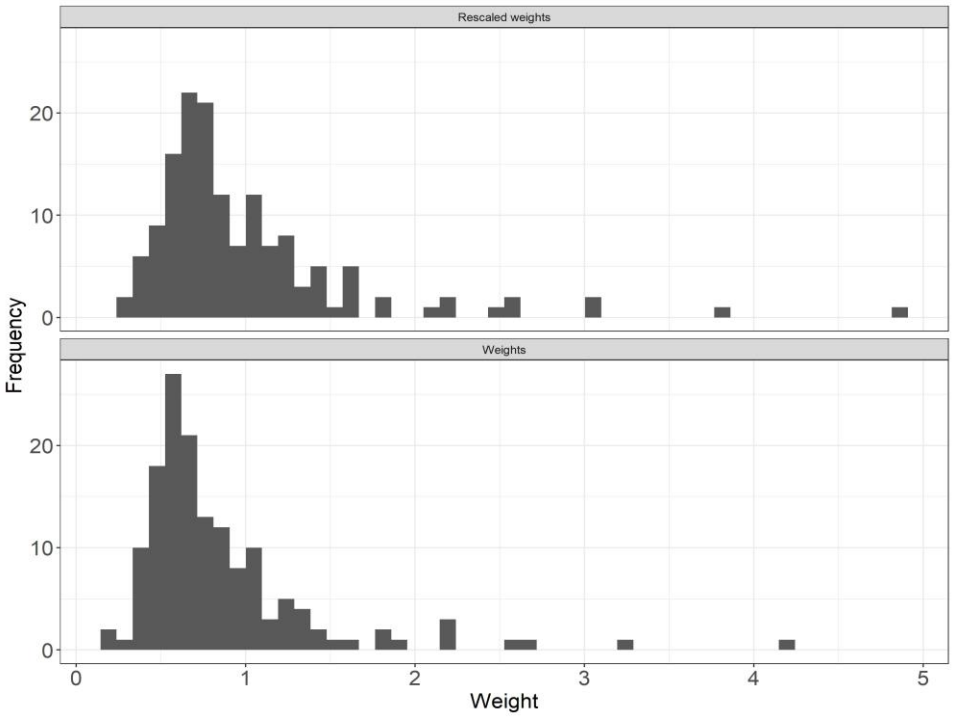
Abbreviations: ITT, intention-to-treat; KM. Kaplan-Meier.
References: IFT analysis of date from OLE study, all patients, Dec 23 DCO (Italfarmaco 2024s)

Model diagnostics unanchored MAIC

Model diagnostics for all givinostat (EPIDYS and Study 51) vs. SoC (UK real-world data) analyses are presented in Figure 29 to Figure 38. These include:

- Histogram of rescaled weights
- Distribution of bootstrapped bootstrapped HRs for each outcome
- Log-cumulative hazards plot for each outcome
- Schoenfeld residuals for proportional hazards assumption for each outcome.

Figure 29: Histogram of rescaled weights: givinostat (EPIDYS and OLE) vs. SoC (UK real-world data)



Loss of ambulation

Figure 30: Bootstrapped hazard ratios for loss of ambulation: givinostat (EPIDYS and OLE) vs. SoC (UK real-world data)

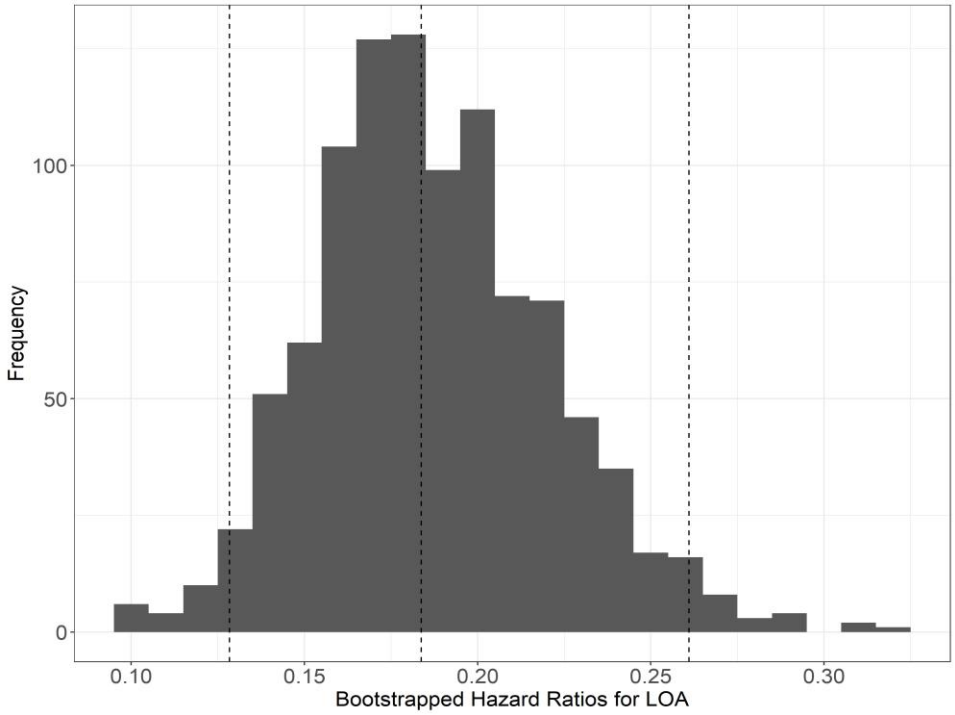


Figure 31: Log-cumulative hazards plot for loss of ambulation: givinostat (EPIDYS and OLE) vs. SoC (UK real-world data)

Figure 32: Schoenfeld residuals for PH assumption for loss of ambulation: givinostat (EPIDYS and OLE) vs. SoC (UK real-world data)

Age at NIV

Figure 33: Bootstrapped hazard ratios for age at NIV: givinostat (EPIDYS and OLE) vs. SoC (UK real-world data)

Figure 34: Log-cumulative hazards plot for age at NIV: givinostat (EPIDYS and OLE) vs. SoC (UK real-world data)

Figure 35: Schoenfeld residuals for PH assumption for age at NIV: givinostat (EPIDYS and OLE) vs. SoC (UK real-world data)

Age at FVC <1L

Figure 36: Bootstrapped hazard ratios for age at FVC <1L: givinostat (EPIDYS and OLE) vs. SoC (UK real-world data)

Figure 37: Log-cumulative hazards plot for age at FVC <1L: givinostat (EPIDYS and OLE) vs. SoC (UK real-world data)

Figure 38: Schoenfeld residuals for PH assumption for age at FVC <1L: givinostat (EPIDYS and OLE) vs. SoC (UK real-world data)

Appendix D. Extrapolation

Extrapolation of survival

The primary data source informing the updated NHM is C-Path D-RSC database, which includes anonymized individual patient data from 11 international data sources, including NH studies, placebo arms of clinical trials, and registry data (Broomfield et al. 2024). Please see Broomfield et al. (2024) for description of NHM. Limited information on extrapolation method of survival in the original NHM is available from the publications, hence not all sections have been populated.

Model

A piecewise exponential parametric model.

Proportional hazards

Not available.

Evaluation of statistical fit (AIC and BIC)

Not available.

Evaluation of visual fit

Not available.

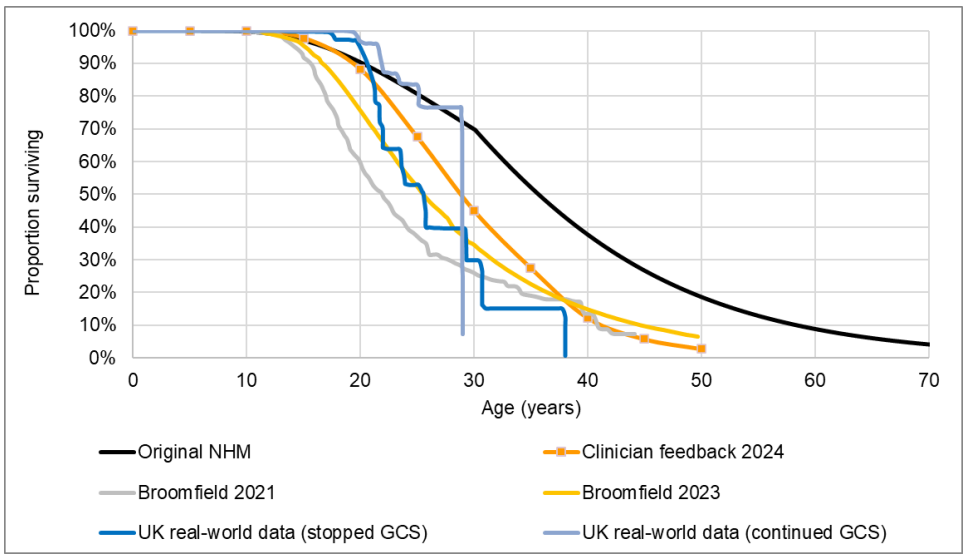
Evaluation of hazard functions

Not available.

Validation and discussion of extrapolated curves

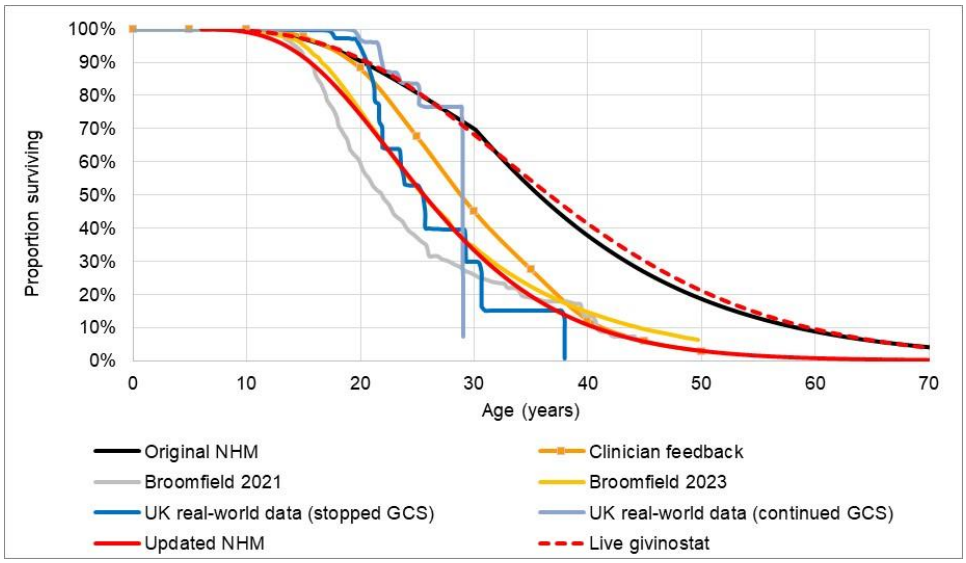
As described in section 8.1, the published NHM was validated against literature, UK real-world data and clinical feedback, and was later updated based on this feedback. Figure 39 presents the comparison of survival from the published NHM (also described in Table 23 in section 8.1). The resulting survival curve after updating the NHM and comparison with external sources as well as the original NHM are described in Figure 40 (also presented in Table 24 in section 8.1).

Figure 39: A comparison of survival from the published NHM with the literature, UK real-world data, and clinician feedback



Abbreviations: GCS: glucocorticoids; NHM: natural history model

Figure 40: A comparison of survival from the updated NHM with external sources and the published NHM



Abbreviations: GCS: glucocorticoids; NHM: natural history model

Adjustment of background mortality

Background mortality using Danish normal population mortality from Medicinrådet were only included to calculate transition probability from health state 1 to death (adjusted such that mortality could not be lower than the general population).

Adjustment for treatment switching/cross-over

Not applicable.

Waning effect

Not applicable.

Cure-point

Not applicable, no treatment for DMD is considered a curative treatment but rather delays time to DMD progression.

Extrapolation of Loss of Ambulation, Non-Invasive Ventilation, and FVC<1L (MAIC)

Data input

Please see section 7.

Model

Parametric survival model with log-normal distribution.

Proportional hazards

Evaluation of proportional hazards was conducted using log-cumulative hazards plot and Schoenfeld residuals, presented in Figure 41–Figure 46.

Figure 41: Log-cumulative hazards plot for loss of ambulation: givinostat (EPIDYS and OLE) vs. SoC (UK real-world data)

Figure 42: Schoenfeld residuals for PH assumption for loss of ambulation: givinostat (EPIDYS and OLE) vs. SoC (UK real-world data)

Figure 43: Log-cumulative hazards plot for age at NIV: givinostat (EPIDYS and OLE) vs. SoC (UK real-world data)

Figure 44: Schoenfeld residuals for PH assumption for age at NIV: givinostat (EPIDYS and OLE) vs. SoC (UK real-world data)

Figure 45: Log-cumulative hazards plot for age at FVC <1L: givinostat (EPIDYS and OLE) vs. SoC (UK real-world data)

Figure 46: Schoenfeld residuals for PH assumption for age at FVC <1L: givinostat (EPIDYS and OLE) vs. SoC (UK real-world data)

Evaluation of statistical fit (AIC and BIC)

The AIC and BIC indicate that the log-normal, generalized gamma, and gamma parametric curves provide the best fit to the loss of ambulation, non-invasive ventilation, and FVC<1L MAIC-weighted givinostat data – with a difference less than three across AIC and BIC scores. Aligned with the lowest AIC and BIC scores, the medians predicted from the log-normal parametric curve are used in the SOLVER calculations when estimating the HRs relevant to transitions underpinning the model structure.

Table 72: AIC and BIC values corresponding to independent parametric curves fit to the MAIC-weighted Kaplan-Meier data for givinostat

	AIC	BIC	Rank (AIC)	Rank (BIC)
Loss of ambulation				
Exponential	356	359	7	7
Weibull	290	296	5	5
Lognormal	283	289	2	1
Loglogistic	286	292	4	4
Gompertz	299	305	6	6
Generalised Gamma	282	291	1	3
Gamma	285	291	3	2
Non-invasive ventilation				
Exponential	386	389	7	7
Weibull	320	326	5	5
Lognormal	312	318	2	1
Loglogistic	316	322	4	4
Gompertz	328	334	6	6

	AIC	BIC	Rank (AIC)	Rank (BIC)
Generalised Gamma	311	320	1	3
Gamma	314	320	3	2
FVC<1L				
Exponential	405	408	7	7
Weibull	338	344	5	5
Lognormal	331	337	2	1
Loglogistic	334	340	4	4
Gompertz	347	353	6	6
Generalised Gamma	330	339	1	3
Gamma	333	339	3	2

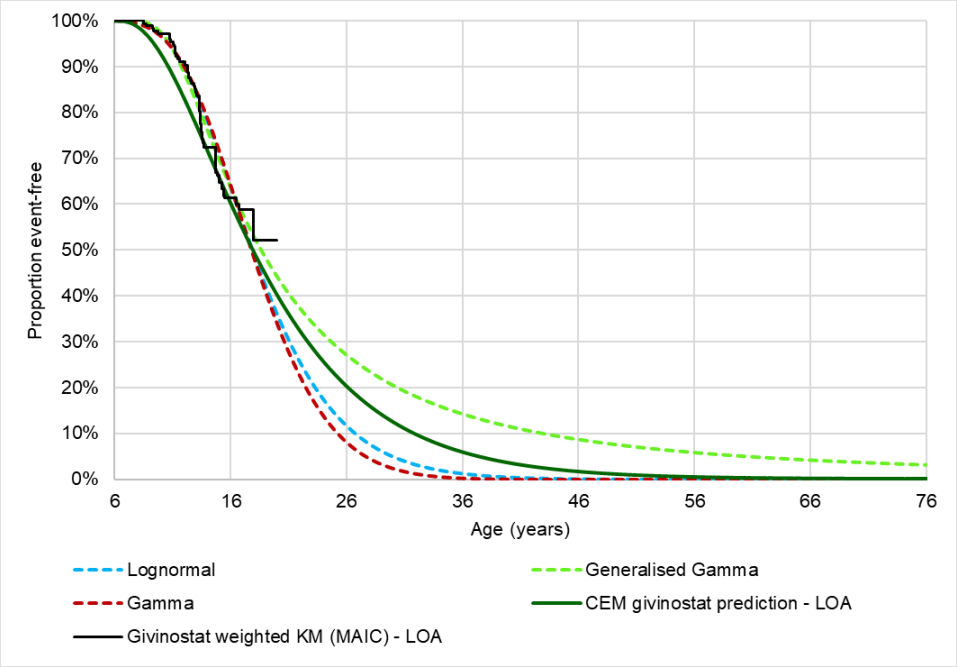
Abbreviations: AIC: Akaike information criterion; BIC: Bayes information criterion; FVC: forced vital capacity; MAIC: matched adjusted indirect comparison.

Evaluation of visual fit

Predicted time to loss of ambulation, time to ventilation, and time to FVC<30% are presented in Figure 47–Figure 49 for the best fitting parametric curves to the MAIC-weighted Kaplan-Meier curves. Both gamma, log-normal and generalised gamma fit the Kaplan-Meier curve well in the first 10 years. Lognormal and gamma distributions estimate lower event-free rates during the period beyond Kaplan-Meier data. The predicted proportions event free in the CEM are depicted in the figures, which are estimated by applying the HRs to the natural history data. The CEM predicted event free rates is approximately average of log-normal, gamma, and generalised gamma.

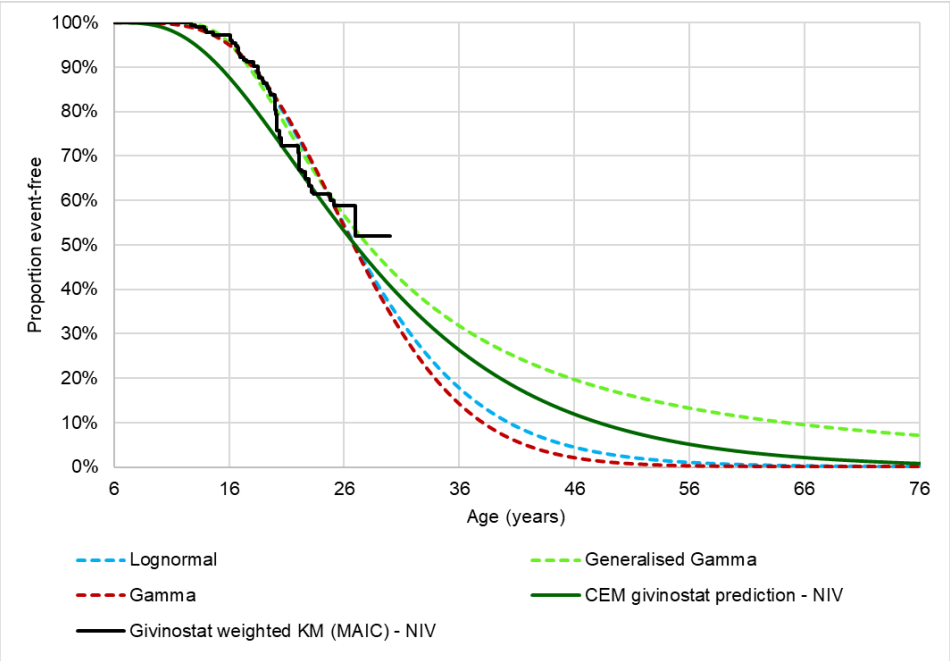
Median values for loss of ambulation, ventilation, and FVC are presented in Table 73.

Figure 47: Comparison of the predicted time to loss of ambulation with the best fitting parametric curves fit to the MAIC-weighted givinostat loss of ambulation data



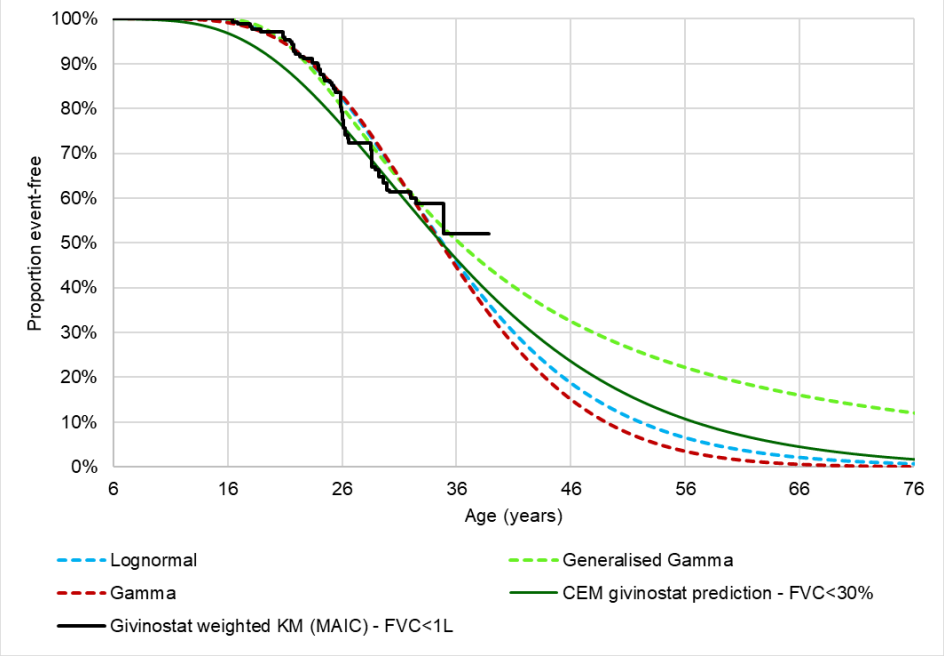
Abbreviations: KM: Kaplan-Meier; LOA: loss of ambulation, MAIC: matched adjusted indirect comparison.

Figure 48: Comparison of the predicted time to ventilation with the best fitting parametric curves fit to the MAIC-weighted givinostat non-invasive ventilation data



Abbreviations: KM: Kaplan-Meier; MAIC: matched adjusted indirect comparison; NIV: non-invasive ventilation.

Figure 49: Comparison of the predicted time to FVC<30% with the best fitting parametric curves fit to the MAIC-weighted givinostat FVC<1L data



Abbreviations: FVC: forced vital capacity; KM: Kaplan-Meier; MAIC: matched adjusted indirect comparison.Validation of modelled disease progression

Table 73: Median age at event corresponding to independent parametric curves fit to the MAIC-weighted Kaplan-Meier data for givinostat

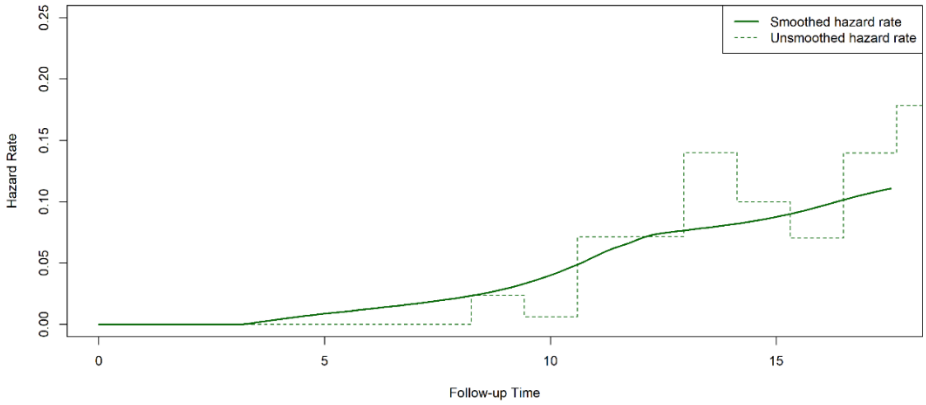
	Median	Lower bound	Upper bound

Loss of ambulation			
Exponential	****	****	****
Weibull	****	****	****
Lognormal	****	****	****
Loglogistic	****	****	****
Gompertz	****	****	****
Generalised Gamma	****	****	****
Gamma	****	****	****
Non-invasive ventilation			
Exponential	****	****	****
Weibull	****	****	****
Lognormal	****	****	****
Loglogistic	****	****	****
Gompertz	****	****	****
Generalised Gamma	****	****	****
Gamma	****	****	****
[redacted]			
Exponential	****	****	****
Weibull	****	****	****
Lognormal	****	****	****
Loglogistic	****	****	****
Gompertz	****	****	****
Generalised Gamma	****	****	****
Gamma	****	****	****

Abbreviations: AIC: Akaike information criterion; BIC: Bayes information criterion; FVC: forced vital capacity; MAIC: matched adjusted indirect comparison.

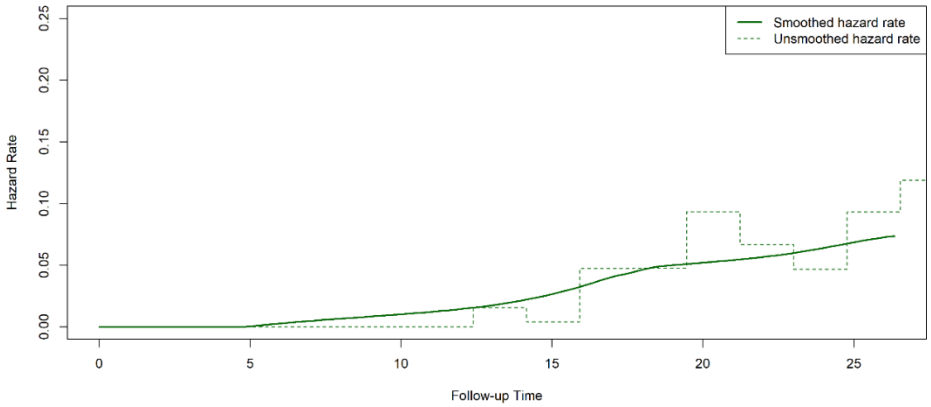
Evaluation of hazard functions

Figure 50: Hazards corresponding to the MAIC-weighted Kaplan-Meier data for age at loss of ambulation



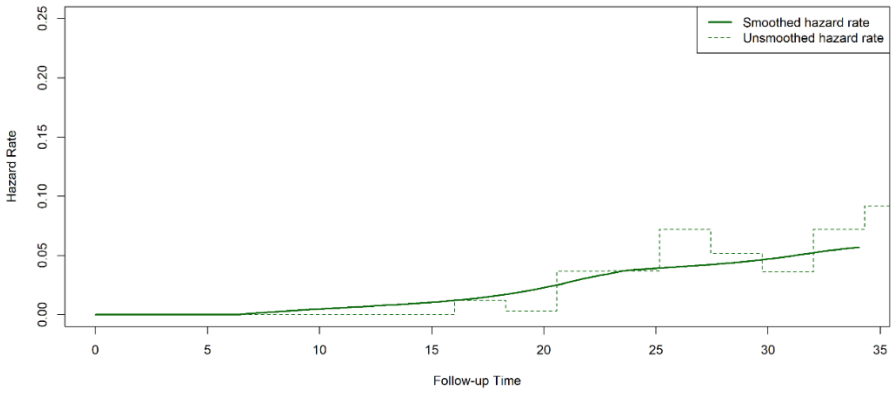
Abbreviations: MAIC: matched adjusted indirect comparison.

Figure 51: Hazards corresponding to the MAIC-weighted Kaplan-Meier data for age at non-invasive ventilation



Abbreviations: MAIC: matched adjusted indirect comparison.

Figure 52 Hazards corresponding to the MAIC-weighted Kaplan-Meier data for age at FVC<1L



Abbreviations: FVC: forced vital capacity; MAIC: matched adjusted indirect comparison.

Validation and discussion of extrapolated curves

The NHM underwent extensive validation as part of the updates to ensure that the NHM informing the CEM is externally valid and relevant to clinical practice. To ensure the relevance to Danish clinical practice, the model's predictions for the median age at the different disease milestones were also validated by a Danish clinician (Italfarmaco 2024c).

Additional data have been obtained from the UK NorthStar registry for the number of patients who are ambulant and non-ambulant across ages 6–18 years; these data are presented in Table 74 and compared to the model predictions for standard of care (GCs alone) (Italfarmaco 2024h). The UK North Star registry is part of the UK North Star Programme which is the world's largest natural history study of boys and men with Duchenne muscular dystrophy (DMD) and a clinical network of UK-wide healthcare professionals focusing on the best clinical management of DMD (Muscular Dystrophy UK 2025). They have developed the North Star Ambulatory assessment, which is now included in the international guidelines in Europe (Birnkrant et al. 2018a, Birnkrant et al. 2018c, Birnkrant et al. 2018d).

The base case model predictions are shown to closely align with the NorthStar data; it is expected that the model predictions are slightly higher than the NorthStar data based on the requirement for ambulant status at baseline (age 6).

Table 74: A comparison of NorthStar ambulation status data with the GCs model predictions*

Age	NorthStar data		GCs – Model predictions	
	Ambulant	Non-ambulant	Ambulant	Non-ambulant
6	21 (95.5%)	1 (4.5%)	100%	0%
7	25 (92.6%)	2 (7.4%)	96%	4%
8	41 (95.3%)	2 (4.7%)	88%	12%
9	29 (76.3%)	9 (23.7%)	78%	22%
10	43 (79.6%)	11 (20.4%)	68%	32%
11	42 (72.4%)	16 (27.6%)	58%	42%
12	30 (45.5%)	36 (54.5%)	49%	51%
13	34 (47.9%)	37 (52.1%)	41%	59%
14	17 (30.4%)	39 (69.6%)	34%	66%
15	19 (28.4%)	48 (71.6%)	29%	71%
16	16 (22.9%)	54 (77.1%)	24%	76%
17	17 (25.4%)	50 (74.6%)	20%	80%
18+	30 (13.8%)	188 (86.2%)	17%	83%

Note: *these data reflect a snapshot in time and are not cumulative.

Abbreviations: GCs: glucocorticoids

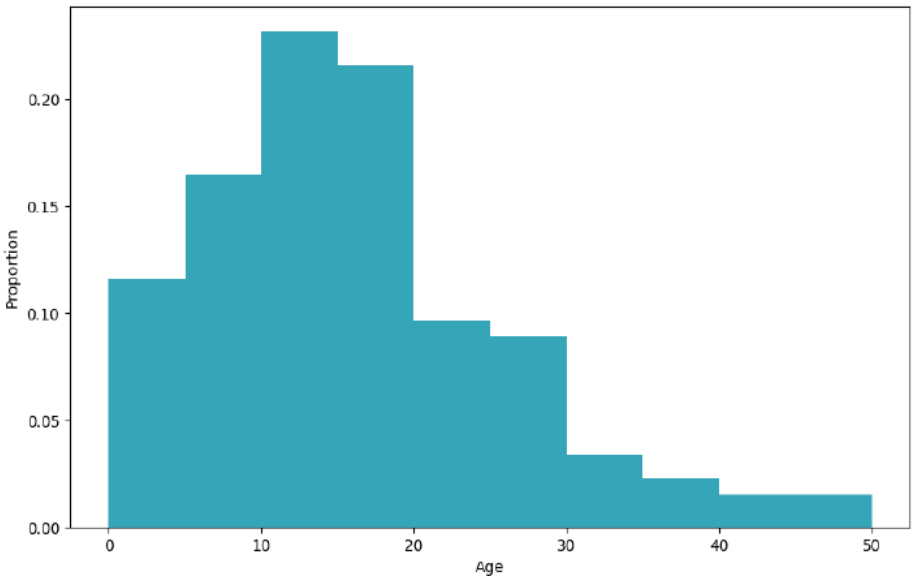
Additional data have also been obtained through a descriptive study using the Hospital Episodes Statistics (HES) dataset to explore the healthcare utilisation, costs, and life expectancy associated with standard of care for DMD in England (Italfarmaco UK 2024, Roberts et al. 2024).

A total of 7,718 patients were identified in the HES data set with ICD-10 code for muscular dystrophy (G71.0) recorded in any of the 20 diagnosis fields from April 2019 to March 2024. Six explicit exclusion criteria were applied to distinguish patients with DMD from the cohort: (1) female patients were excluded as DMD predominantly occurs in males (N=2,752 excluded), (2) patients diagnosed after eight years of age were excluded as DMD is predominantly diagnosed in early childhood (N=24 excluded), (3) patients aged over 50 years of age were excluded as, based on clinical feedback, it is unlikely that many patients with DMD will survive beyond age 50 (N=1,730 excluded), (4) patients with ICD-10 codes for other forms of muscular disorders were excluded (N=547 excluded), (5) patients aged over 20 years of age without recorded ambulation issues were excluded aligned with previous studies and clinical feedback (N=630 excluded), and (6) patients aged over 30 years of age without recorded ventilation issues were excluded aligned with clinical

feedback (N=95). This resulted in 1,937 patients comprising the cohort described in this submission and assumed to represent patients with DMD in England. All disease milestone for the Danish patient population were discussed with a Danish clinicians and it is in line with the above exclusion criteria.

Figure 53 presents the distribution of patients by age group (Italfarmaco 2024f, Italfarmaco 2024g); the mean age across all patients was 16.7 (SD: 9.7). The mean age predicted by the GCs alone arm in the CEM is 18.8 – this closely aligns with the data from the HES study. The HES study identified N=976 patients with abnormal ambulation and N=650 patients who had been ventilated in the previous 5-years. The mean age of patients in the HES data set with abnormal ambulation was 22.7 (SD: 9.5) and with ventilation was 25.4 (SD: 9.6). The mean ages predicted by the GCs alone arm in the CEM for these patients are 22.5 and 24.9, respectively – closely aligning with the data from the HES study.

Figure 53: Study cohort assumed to have DMD in the HES dataset by age group



Abbreviations: DMD: Duchenne muscular dystrophy; HES: Hospital Episode Statistics.

Source: Roberts et al. (2024)

The HES study explores age of death through two methods: (1) analysing known inpatient deaths for patients assumed to have DMD within the past 5-years and (2) analysing presumed deaths of patients assumed to have DMD who have not had recorded activity in the HES data set for the past two years. In method (1), the study identified 116 patients who died in the past five years (April 2019 – March 2024). The average age of death was 28 years across these 116 patients. In method (2), the study identified 40 patients who had no health records in the past two years and who were assumed to have died (April 2022 – March 2024). The average age of death was 23 years across these 40 patients. The average age of death in the CEM is 25.5 – closely aligning with the data from the HES study.

The HES dataset is unable to identify deaths of patients who passed away in the community – this is a key limitation as reportedly a large proportion of patients with DMD die in community settings. Additionally, the presumed death analysis infers that the death of a patient has occurred if they have had a history of recorded care but have not had inpatient, outpatient, or emergency activity in the past two years. Therefore, it is unable to distinguish non-activity in the past two years because of other reasons e.g. the patient has moved to another country. Despite these limitations, the average age of death observed in the HES analyses (23–28 years) aligns with the mean age of death predicted by the CEM for patients treated with GCs alone (27.1).

Table 75 presents the median age patients reach key disease milestones predicted by the CEM; for the GCs alone arm these are aligned with what is seen in Danish clinical practice as well as the UK NorthStar and HES data described above. The values predicted in the givinostat arm align with the median ages at key milestones derived from parametric curves fit to the MAIC-weighted Kaplan-Meier data.

Table 75: Comparison of age milestones from published NHM, updated NHMs, and UK real-world data

Median age at: (in years)	Updated NHM	UK real-world data	Published NHM
Unable to stand from supine	[redacted]	[redacted]	10.2
Loss of ambulation	[redacted]	[redacted]	15.5
Starting ventilation	[redacted]	[redacted]	19.6
Starting full time ventilation	[redacted]	[redacted]	23.9
Death	[redacted]	[redacted]	35.6

Abbreviations: NA: not available; NHM: natural history model

Adjustment of background mortality

Background mortality using Danish normal population mortality from Medicinrådet were only included to calculate transition probability from health state 1 to death (adjusted such that mortality could not be lower than the general population).

Adjustment for treatment switching/cross-over

Not applicable.

Waning effect

Waning effect is not included.

Cure-point

Not applicable, givinostat is not considered a curative treatment but rather delays time to DMD progression.

Appendix E. Serious adverse events

Serious TEAEs by MedDRA

Overall, [redacted] patients in the Duvyzat® (givinostat) group and [redacted] patients in the control group reported at least one serious TEAE. Serious TEAEs in the Duvyzat® (givinostat) group included gastroenteritis, gastroenteritis viral, influenza, abdominal pain, vomiting, chest pain, spinal fracture, dizziness, and rash, all reported by [redacted] patient each. No serious TEAEs were considered related to the study drug or led to withdrawal (Table 76) (Italfarmaco 2022a).

Table 76: Summary of Serious TEAEs by MedDRA System Organ Class and Preferred Term (Safety Analysis Set - overall population)

System organ class Preferred term	Duvyzat® (givinostat) (n=118) Patients (%)	Control group (n=61) Patients (%)
Total number of serious TEAEs	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
Gastroenteritis	[redacted]	[redacted]
Gastroenteritis viral	[redacted]	[redacted]
Influenza	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]
Chest pain	[redacted]	[redacted]
Injury, poisoning, and procedural complications	[redacted]	[redacted]
Spinal fracture	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]
Rash	[redacted]	[redacted]

Abbreviations: MedDRA: Medical Dictionary for Regulatory Activities; N: number of patients in the study population; TEAE: Treatment-Emergent Adverse Event.
Sources: ClinicalTrials.gov (2023a)

Treatment compliance and exposure

Treatment compliance was high, and 95% of boys completed the study. The mean treatment duration was 493 days and was similar in all groups (givinostat, placebo, Target ITT population, and Group B). Mean compliance was greater than 98% in all groups (98.3% for givinostat and 98.1% for placebo overall; 98.7% for givinostat and 98.0% for placebo in the Target ITT population). Dosing was changed to Regimen 2 after 82 (46%) boys had been randomly assigned, but a *post hoc* ANCOVA analysis suggests that this was unlikely to have affected the

results (Mercuri et al. 2024b, Mercuri et al. 2024c). One boy, who was receiving placebo, lost ambulation at Week 60.

Dose modifications and treatment discontinuation

Boys received a flexible-dose regimen in EPIDYS, aimed at maximising efficacy, starting with a high dose that was reduced if treatment was not tolerated (Mercuri et al. 2024b, Mercuri et al. 2024c). In DMD, patients are continually being reviewed and dose modifications for treatments such as GCs are common (Birnkrant et al. 2018a).

In the Overall ITT population (Groups A and B), 72.9% of boys in the givinostat group and [redacted] of boys in the placebo group had dose modifications; these were due to AEs in [redacted] and [redacted], respectively (Italfarmaco 2022a). Givinostat dose modifications included dose increases (6/118; 5.1%), dose reductions (57/118; 48.3%), doses permanently stopped (10/118; 8.5%), doses temporarily stopped (19/118; 16.1%), and doses skipped (47/118; 39.8%), though this did not lead to a loss of efficacy. Of the dose reductions in EPIDYS, [redacted] were driven by a laboratory finding of reversible thrombocytopaenia or hypertriglyceridaemia [redacted] were due to moderate abdominal pain and moderate diarrhoea) (Italfarmaco 2022a).

Givinostat showed a statistically significant positive effect on 4SC despite the dose modifications seen in the study (Mercuri et al. 2024b, Mercuri et al. 2024c). The flexible-dose regimen was successful in that 95% of boys completed the EPIDYS study, there were very few severe AEs, and only 3% boys receiving givinostat discontinued treatment due to AEs (all due to increased blood triglyceride) (Mercuri et al. 2024b, Mercuri et al. 2024c).

AEs

A summary of AEs at 18 months for the Overall ITT EPIDYS population (Groups A and B) is provided in Table 77. Similar proportions of boys had AEs in both groups (112 [95%] of 118 boys receiving givinostat versus 57 [93%] of 61 boys receiving placebo, demonstrating that many of the AEs reported were due to the concomitant therapies, such as GCs, that boys were receiving, rather than being related to givinostat; Table 77) (Mercuri et al. 2024b, Mercuri et al. 2024c). There was no considerable difference in the incidence of AEs based on the total weight-adjusted exposure or based on the starting dose of givinostat (Italfarmaco 2022a). Most AEs in both treatment groups were mild to moderate in severity (91% in the givinostat group and 92% in the placebo group) (Mercuri et al. 2024b, Mercuri et al. 2024c, Italfarmaco 2022a).

The most common AEs in the givinostat group (not necessarily related to the treatment) were diarrhoea, decreased platelet count or thrombocytopaenia, vomiting nasopharyngitis, headache, increased triglycerides and abdominal pain (Table 78). The only severe AE in two or more boys was vomiting (Mercuri et al. 2024b, Mercuri et al. 2024c).

Comparison of short-term safety data (within 3 months of treatment initiation) vs. long-term data (after 3 months of treatment) show that AEs occur more frequently in the first 3 months of treatment (Vucinic et al. 2024). Diarrhoea and vomiting were less frequent in the long-term than the short-term (15.3% vs. 29.7% and 14.4% vs. 21.2% respectively). Likewise, abdominal pain was 8.5% in long-term versus 16.1% in the short-term, and episodes of low platelet count and thrombocytopaenia were less frequent after 3 months of treatment than in the first 3 months of treatment initiation (5.1% vs.14.4% and 6.8% vs.10.2% respectively) (Vucinic et al. 2024).

Table 77: Summary of AEs | EPIDYS Safety population

System organ class Preferred term	Givinostat* (N=118)	Placebo* (N=61)
	Boys (%)	Boys (%)
Total number of AEs	112 (95%)	57 (93%)
Total number of serious AEs	8 (7%)	2 (3%)
Total number of boys with AEs leading to withdrawal	3 (3%)	0
Fatal AEs	0	0
Total number of boys with AEs leading to permanent discontinuation of the study drug	4 (3%)	0
Total number of boys with AEs leading to temporary discontinuation of the study drug	16 (14%)	4 (7%)
Total number of boys with AEs leading to dose reduction	42 (36%)	1 (2%)
Severity[1]		
Mild (Grade 1)	69 (59%)	39 (64%)
Moderate (Grade 2)	38 (32%)	17 (28%)
Severe[2] (Grade 3)	5 (4%)	1 (2%)
Life-threatening[3] (Grade 4)	0	0
Death related to AE (Grade 5)	0	0

Notes: [1]If a boy experienced more than one AE, the boy was counted once at the most severe or most related event; [2]included severe or medically significant but not immediately life-threatening AEs; [3]included severe or life-threatening AEs; *all boys were also receiving systemic GCs, in a dose and regimen that was to remain unchanged over the follow-up period.
Abbreviations: AE: adverse event; n: number of boys in the study population;.
References: Mercuri et al. (2024b), Mercuri et al. (2024c), Italfarmaco (2022a)

Table 78: Most common AEs | EPIDYS Safety population

AEs	Givinostat* (N=118)	Placebo* (N=61)
Diarrhoea	43 (36%)	11 (18%)
Decreased platelet count or thrombocytopenia	38 (32%)	0
Vomiting	34 (29%)	8 (13%)
Nasopharyngitis	31 (26%)	19 (31%)
Headache	28 (24%)	14 (23%)
Increased blood triglyceride concentration or hypertriglyceridaemia	27 (23%)	4 (7%)
Abdominal pain	25 (21%)	9 (15%)
Upper abdominal pain	17 (14%)	7 (11%)
Fall	15 (13%)	13 (21%)

Pyrexia	15 (13%)	5 (8%)
Cough	13 (11%)	9 (15%)
Pain in extremity	8 (7%)	7 (11%)
Upper respiratory tract infection	7 (6%)	8 (13%)
Back pain	6 (5%)	8 (13%)
Rhinitis	6 (5%)	7 (11%)

Notes: Data are number of boys (%); events are listed by % of boys; data are grouped by treatment received at baseline; table shows MedDRA preferred terms that occurred in ≥10% boys in either group for AEs or AEs leading to dose reduction; ≥5% boys in either group for treatment-related AEs; and ≥2 boys in either group for AEs leading to treatment interruption or withdrawal, serious, and severe AEs; the thresholds were selected for clarity of reporting and to highlight the most commonly reported MedDRA preferred terms only; the severity of the AEs was assessed and graded by the investigators according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (June 14, 2010); *all boys were also receiving systemic GCs, in a dose and regimen that was to remain unchanged over the follow-up period.
Abbreviations: AE: adverse events; MedDRA: Medical Dictionary for Regulatory Activities; N: number of boys in the study population.
References: Mercuri et al. (2024b), Mercuri et al. (2024c)

Treatment-related AEs

Treatment-related AEs (and AEs leading to dose reduction) were more common with givinostat than with placebo (Table 79), although these were typically known to be associated with givinostat treatment (e.g. diarrhoea, thrombocytopaenia, and hypertriglyceridaemia) (Mercuri et al. 2024b, Mercuri et al. 2024c). In the givinostat group, 81/118 boys (69%) had an AE that was considered to be treatment-related, versus 17/61 boys (28%) in the placebo group (Mercuri et al. 2024b, Mercuri et al. 2024c).

None of the severe or serious AEs were treatment-related or resulted in study withdrawal (Mercuri et al. 2024b, Mercuri et al. 2024c).

Table 79: Treatment-related AEs | EPIDYS Safety population

Treatment-related AEs	Givinostat* (N=118)	Placebo* (N=61)
Treatment-related AEs	81 (69%)	17 (28%)
Decreased platelet count or thrombocytopaenia	37 (31%)	0
Increased blood triglyceride concentration or hypertriglyceridaemia	26 (22%)	4 (7%)
Diarrhoea	25 (21%)	2 (3%)
Abdominal pain	16 (14%)	2 (3%)
Upper abdominal pain	9 (8%)	1 (2%)
Vomiting	7 (6%)	0

Notes: Data are number of boys (%); events are listed by % of boys; data are grouped by treatment received at baseline; table shows MedDRA preferred terms that occurred in ≥5% boys in either group for treatment-related AEs; *all boys were also receiving systemic GCs, in a dose and regimen that was to remain unchanged over the follow-up period.
Abbreviations: AE: adverse events; MedDRA: Medical Dictionary for Regulatory Activities; N: number of boys in the study population.
References: Mercuri et al. (2024b), Mercuri et al. (2024c)

Selected safety events of clinical interest

Diarrhoea, decreased platelet count, and hypertriglyceridaemia are recognised AEs of givinostat and can generally be managed by dose reduction or interruption (as was the case in EPIDYS as 95% of boys completed the study, and treatment compliance was high) (Mercuri et al. 2024b, Mercuri et al. 2024c). Platelet reduction is a known AE associated with HDAC inhibitors, including givinostat, and is considered to be related to their pharmacological effect (Bettica et al. 2016).

Diarrhoea

Diarrhoea was more common in the givinostat group, occurring in 43 (36%) boys versus 11 (18%) in the placebo group (Mercuri et al. 2024b, Mercuri et al. 2024c). This was considered to be treatment-related in 21% of the givinostat group (Mercuri et al. 2024b, Mercuri et al. 2024c). One boy in the givinostat group withdrew from the study due to diarrhoea (Italfarmaco 2022a).

Decreased platelets

A reduction in mean platelet count between baseline and 18 months was observed in boys receiving givinostat but not in those receiving placebo, although platelet counts were highly variable (Mercuri et al. 2024b, Mercuri et al. 2024c). In the givinostat group, 67 (57%) of 118 boys had a shift from normal to low platelet counts during the study (compared with three [5%] of 61 in the placebo group); in 33 (28%) of these 118, the dose of givinostat was reduced due to decreased platelet count (23 [42%] of 55 on Regimen 1 and ten [16%] of 63 on Regimen 2) (Mercuri et al. 2024b, Mercuri et al. 2024c). The thrombocytopaenia events leading to dose reduction were mild and reversible; no events resulted in study withdrawal and none was associated with clinical signs such as excessive bleeding (Mercuri et al. 2024b, Mercuri et al. 2024c, Italfarmaco 2022a).

Increased triglyceride levels

Mean triglyceride concentrations increased from baseline to 18 months; 70 (59%) of 118 boys receiving givinostat had a shift from normal to high triglyceride concentrations during this time, compared with 30 (49%) of 61 boys receiving placebo (Mercuri et al. 2024b, Mercuri et al. 2024c). The AEs of increased blood triglyceride concentrations or hypertriglyceridaemia were more common with givinostat (27 [23%] of 118 boys) than with placebo (four [7%] of 61 boys); two such events, each in a boy receiving givinostat, resulted in study withdrawal, but were not severe or serious AEs (Mercuri et al. 2024b, Mercuri et al. 2024c). Events of hypertriglyceridaemia leading to dose reduction (n=10) were mild in two cases and moderate in the remaining eight, with the highest value being <3× the upper limit of normal (Italfarmaco 2022a).

Only minor changes were observed in other haematological and blood chemistry parameters. Vital signs, electrocardiogram, and pulmonary function were similar in the givinostat and placebo groups (Mercuri et al. 2024b, Mercuri et al. 2024c).

QTc interval prolongation

Givinostat can cause prolongation of QTc interval. However, no Fridericia corrected QT interval (QTcF) prolongation was recorded in either the givinostat or placebo groups, and other ECG parameters remained stable throughout the study (Italfarmaco 2022a).

Additional analysis of givinostat safety data

The company has conducted an additional limited assessment of safety outcomes in DMD patients who have become non ambulant while on treatment with either placebo or givinostat in Study 43, EPIDYS and the OLE (Italfarmaco 2024a).

A total of [redacted] boys/young men with DMD have become non-ambulant while participating in givinostat DMD clinical studies (Italfarmaco 2024a). Overall, patients experienced [redacted] TEAEs following loss of ambulation compared with before loss of ambulation (Table 80), which is expected considering that the mean duration of exposure in this group of patients was approximately 60 months (Italfarmaco 2024a) and many of the more common TEAEs associated with givinostat (e.g. platelet count reductions) are most frequently experienced by patients within the first few months of treatment (Vucinic et al. 2024). Review of platelet and triglyceride laboratory results and ECGs revealed [redacted] safety concerns in patients who lost ambulation while on treatment (Italfarmaco 2024a).

These analyses show that loss of ambulation had no negative effects on the safety profile of givinostat (Italfarmaco 2024a).

Table 80: Overview of AEs in boys/young men who lost ambulation while receiving givinostat (safety set)

AE category	Givinostat overall (N=34)	
	Pre-loss of ambulation	Post-loss of ambulation
Number of AEs (events/patient years)	[redacted]	[redacted]
Number of boys/young men with AEs (n, %)	[redacted]	[redacted]
Number of SAEs (event/patient years)	[redacted]	[redacted]
Number of boys/young men with SAEs (n, %)	[redacted]	[redacted]
Number of severe AEs (event/patient years)	[redacted]	[redacted]
Number of boys/young men with severe AEs (n, %)	[redacted]	[redacted]
Number of AESIs (event/patient years)	[redacted]	[redacted]
Number of boys/young men with AESIs (n, %)	[redacted]	[redacted]
Number of AEs leading to discontinuation (event/patient years)	[redacted]	[redacted]
Number of boys/young men with AEs leading to discontinuation (n, %)	[redacted]	[redacted]
Number of AEs leading to death (event/patient years)	[redacted]	[redacted]
Number of boys/young men with AEs leading to death (n, %)	[redacted]	[redacted]
Number of treatment-related AEs (n, %)	[redacted]	[redacted]
Number of boys/young men with treatment-related AEs (n, %)	[redacted]	[redacted]

Notes: AEs with start date ≥date of first study medication intake are presented in this table; loss of ambulation is defined in the ISE SAP; considering the limited number of placebo patients under the defined analysis set, only givinostat patients have been included in this summary; AEs with start date ≥date of loss of ambulation are presented in the post-loss column; AEs with start date <date of loss of ambulation are presented in the pre-loss column; patient-years are calculated separately for pre- and post-loss of ambulation period.
Abbreviations: AE: adverse events; AESI: adverse event of special interest; N: number of boys in the study population, SAE: serious adverse event.
References: Excerpt from D120 EMA responses 2024 (Italfarmaco 2024a)

Overview of safety events in OLE

Table 81: Overview of safety events (Mean treatment duration 1,177 days in OLE)

	OLE		
	Givinostat (n=119)	**Delayed givinostat (n=58)**	**Givinostat naïve (n=30)**
Number of adverse events, n	1600	821	372
Number and proportion of patients with ≥1 adverse events, n (%)	117 (98.3)	56 (96.6)	30 (100)
Number of serious adverse events*, n	38	19	7
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	32 (26.9)	14 (24.1)	6 (20.0)
Number of CTCAE grade ≥ 3 events, n	N/A	N/A	N/A
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	28 (23.5)	6 (10.3)	5 (16.7)
Number of adverse reactions, n	302	177	144
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	82 (68.9)	45 (77.6)	23 (76.7)
Number and proportion of patients who had a dose reduction, n (%)	24 (20.2)	17 (29.3)	4 (13.3)
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	N/A	N/A	N/A
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	4 (3.4)	2 (3.4)	1 (3.3)

Safety conclusions

EPIDYS and the ongoing OLE study confirm that givinostat has a predictable safety profile, consistent with previous studies (Italfarmaco 2022a, Italfarmaco 2024s, Italfarmaco 2019). Treatment compliance is high and there have been no reported life-threatening AEs, or deaths related to givinostat treatment (Italfarmaco 2022a, Italfarmaco 2024s). Givinostat was given in addition to the steroids that was also in the placebo arm of the EPIDYS study, therefore AEs due to steroid treatment occur in both treatment arms. The additional givinostat-related AEs of diarrhoea, thrombocytopaenia and decreased platelet count, and increased blood triglycerides are generally manageable through dose modifications and typically occur more frequently in the first 3 months of treatment (Mercuri et al. 2024b, Mercuri et al. 2024c, Vucinic et al. 2024).

Appendix F. Health-related quality of life

F.1 EPIDYS trial

In EPIDYS trial the PODCI questionnaire was used, in the CEM health states utilities were derived from Audhya et al. (Audhya et al. 2023b), identified through a SLR, further described in Appendix I.

Table 82: Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
PODCI	EPIDYS	A total of 5 subscales (upper extremity function; transfer and basic mobility; sports and physical functioning; pain/comfort and happiness) and 1 global function scale were calculated from the questionnaire.
PedsQL	OLE	The Pediatric Quality of Life Inventory (PedsQL) is a brief measure of health-related quality of life in children and young people. The measure can be completed by parents (the Proxy Report) as well as children and young people (the Self-Report).

Abbreviations: PedsQL: Paediatric Quality of Life Inventory; PODCI: Pediatric Outcome Data Collection Instrument

Presentation of the health-related quality of life measured by PODCI

Study design and measuring instrument

PODCI

In EPIDYS, QoL was measured via the American Academy of Orthopaedic Surgeons Pediatric Musculoskeletal Function Instrument, also referred to as PODCI. The PODCI is comprised of several dimensions that assess upper extremity function, transfers and mobility, physical function and sports, comfort/pain (pain-free), and happiness. There is also a scale for global functioning, which is a combination of the 3 function subscales and comfort (Italfarmaco 2020).

A total of 5 subscales (upper extremity function; transfer and basic mobility; sports and physical functioning; pain/comfort and happiness) and 1 global function scale were calculated from the questionnaire. The endpoints of interest were the change from baseline to 18 months in the standardised scores for each subscale and the global function scale, as completed by the parent and the boy (Italfarmaco 2020, Italfarmaco 2022a).

PedsQL

In the OLE study, the PedsQL was selected to measure QoL, completed by parents/caregivers (the Proxy Report) and by boys/young men (the Self-Report); the study did not directly assess parent/caregiver HRQoL but patient HRQoL as perceived by parent/caregiver. PedsQL total and dimension score and change from baseline over time were analysed for both PedsQL-Child and PedsQL-Parent. The higher numerically PedsQL score indicates better QoL, thus an increase in score indicates and improvement in QoL (Italfarmaco 2024s).

Data collection

PODCI

The PODCI (global function scale) was administered to the parent/legal guardian of subjects. Measurements were made on the Target population at the screening visit, at 12 months and at 18 months (Italfarmaco 2020).

Pattern of missing data and completion

Time point	HRQoL population N=120	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients who completed)
Baseline	118	2 (1.7)	120	118 (98.3)
Month 12	106	14 (11.7)	118	106 (89.8)
Month 18	112	8 (7.1)	118	112 (94.9)

PedsQL

Measurements of PedsQL were made in the ITT Analysis set at baseline and at month 12, 24, 36, 48, 60, and 72 (Italfarmaco 2024s).

Table 83: Pattern of missing data and completion

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients who completed)
Baseline	207	7 (3%)	200	200 (97%)
Month 12	207	6 (3%)	201	201 (97%)
Month 24	207	18 (9%)	189	189 (91%)
Month 36	207	73 (35%)	134	134 (64%)
Month 48	207	150 (72%)	57	57 (28%)
Month 60	207	195 (94%)	12	12 (6%)
Month 72	207	201 (97%)	6	6 (3%)

HRQoL results

PODCI

In EPIDYS, givinostat treatment showed a trend towards a reduction in the decline of the HRQoL, assessed using the Pediatric Outcomes Data Collection Instrument (PODCI), for boys with DMD at 18 months when compared with the placebo group (Italfarmaco 2022a). An analysis of standardised global function scale scores from the PODCI by change from baseline to 18 months is presented in Table 84 for the Target Population in the ITT analysis set. The difference in LS means (givinostat-placebo) of standardised global function scale scores from the PODCI was not statistically significant (LS mean difference [givinostat-placebo]: 2.96; p-value: 0.1824) for change from baseline at 18 months. The trend in PODCI global function scale scores over time is shown in Table 85 and Figure 54.

Table 84: Analysis of Standardised Global Function Scale Scores From the PODCI, Change From Baseline to 18 Months (ITT Analysis Set – Target Population)

Statistics	Givinostat (N=81)	Placebo (N=39)
Number of subjects included in analysis, n (%)	81 (100.0)	39 (100.0)
LS mean (95% CI)	-4.63 (-7.109, -2.155)	-7.59 (-11.173, -4.011)
Difference in LS means (givinostat-placebo) (95% CI)	2.96 (-1.4111, 7.331)	

Abbreviations: CI: Confidence interval; LS: Least square

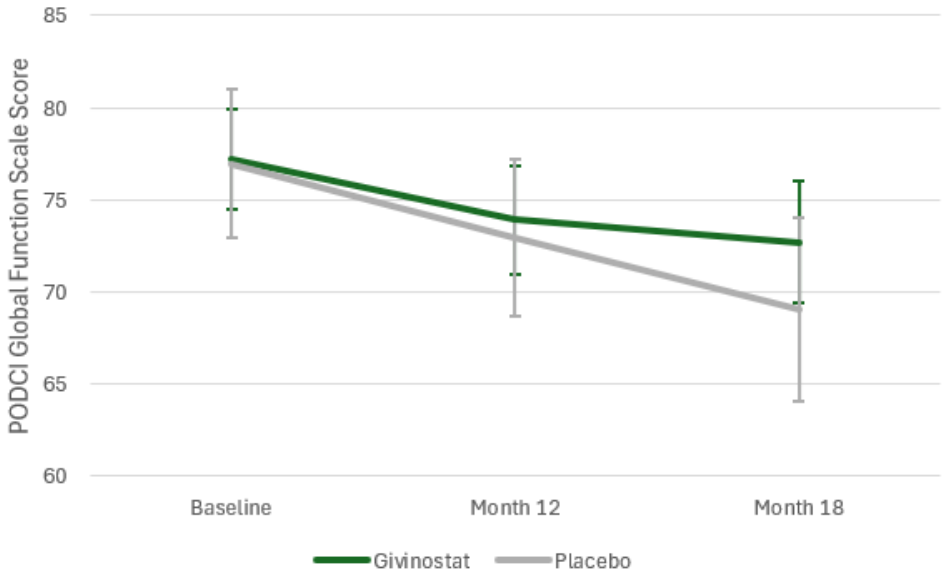
Table 85: HRQoL PODCI Global function scale, summary statistics

	Intervention		Comparator		Intervention vs. comparator
	N=81	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline	81	77.17 (1.40)	39	76.95 (2.06)	0.228 (-4.66, 5.11), ns
Month 12	81	73.91 (1.49)	39	72.93 (2.18)	0.972 (-4.23, 6.17), ns
Month 18	81	72.70 (1.70)	39	69.02 (2.54)	3.68 (-2.30, 9.67), ns

Abbreviations: ns: non-significant.

References: Italfarmaco (2024s)

Figure 54: PODCI Global function scale scores from baseline until Month 18 (EPIDYS Target ITT population)



Abbreviations: ITT: Intention to treat; PODCI: Paediatric Outcome Data Collection Instrument.

PedsQL

Table 86 and Figure 55 presents the PedsQL total score at baseline and change from baseline at month 12, 24, 36, 48, 60, and 72. The higher numerically PedsQL score indicates better QoL, thus an increase in score indicates and improvement in QoL (Italfarmaco 2024s).

Table 86: Summary of Paediatric Quality of Life Inventory (PedsQL) Total and Dimension Score and Change from Baseline over Time (OLE ITT population)

				Change from baseline	
	N	Mean	SD	Mean	SD
Subject Total Score					
Baseline	200	******	*******	*	*
Month 12	201	******	*******	******	*******
Month 24	189	******	*******	******	******
Month 36	134	******	*******	******	******
Month 48	57	******	*******	******	******
Month 60	12	******	*******	******	******
Month 72	6	******	*******	*****	******
********** ***** *****					
Baseline	200	******	*******	*	*
Month 12	201	******	*******	******	******
Month 24	189	******	*******	******	******
Month 36	134	******	*******	******	******
Month 48	57	******	*******	******	******
Month 60	12	******	*******	******	******
Month 72	6	******	*******	*****	******

Abb**Abbreviations**: SD: Standard deviation.

Figure 55: PedsQL Total and dimension score from baseline until Month 72 (ITT population)

Abbreviations: BL: Baseline; PedsQL: Paediatric Quality of Life Inventory

F.2 Other sources of HRQoL in DMD

Landfeldt et al. (2017a) considered three state-transition models to evaluate the cost-effectiveness of a hypothetical treatment for DMD compared to ECM in a UK setting. The utility inputs informing the models were based on a cross-sectional, observational study conducted by the authors and published across four publications (Landfeldt et al. 2016b, Landfeldt et al. 2016a, Landfeldt et al. 2014, Landfeldt et al. 2015).

The study assessed caregiver HRQoL using the EQ-5D-3L. EQ-5D utilities were derived using the UK value set, which is based on preference data collected through the time-tradeoff method from 2,997 randomly selected members of the adult general population in England, Scotland, and Wales. For use in the state transition models presented in Landfeldt et al. (2017a), the utility data were mapped to the specified model states by fitting generalised linear regression models (GLMs) – as described in Landfeldt et al. (2015). Table 87 presents the resulting utilities used in the published CEMs.

The Landfeldt publications also report on patient HRQoL. These data are shown Table 87 or comparison with the caregiver utilities and to align with previous NICE submissions in DMD; previous NICE submissions have used the Landfeldt patient utilities either in the base case or in a scenario (NICE 2023a, NICE 2025). However, these data are measured through proxy-assessment by the primary caregivers using the HUI questionnaire. The HUI is a generic HRQoL instrument encompassing 16 questions covering eight dimensions (hearing, speech, ambulation/mobility, pain, dexterity, self-care, emotion, and cognition) and has been validated for proxy assessments in ages 5 years and older. Patient utilities were derived using the HUI Mark 3 multi-attribute health status classification system, which is based on preference data collected using the standard gamble method and a visual analogue scale from 256 randomly selected members of the general population in Hamilton, Ontario, Canada.

Table 87: Utilities sourced from Landfeldt et al. 2017.

	Utilities	
	Patient*	Caregiver
Model 1 (DMDSAT)		
Initial score	0.879 (0.037)	0.562 (0.016)
Per lost score (multiplier)	0.905 (1.003)	0.995 (1.001)
Model II (ambulatory status)		
Early ambulatory	0.699 (0.036)	0.858 (0.017)
Late ambulatory	0.607 (0.029)	0.839 (0.017)
Early non-ambulatory	0.224 (0.014)	0.784 (0.021)
Late non-ambulatory	0.146 (0.010)	0.810 (0.018)
Model III (ventilation status)		
None	0.518 (0.027)	0.837 (0.014)
Nighttime	0.129 (0.017)	0.775 (0.030)
Day and nighttime	0.051 (0.010)	0.774 (0.033)

*Collected using the HUI-3.

Abbreviations: DMDSAT, Duchenne muscular dystrophy Functional Ability Self-Assessment Tool.

Source: Landfeldt et al. (2017a)

BOI health-related quality-of-life study

In addition to the SLR, a burden of illness (BOI) study has been conducted as part of Project HERCULES – these data have not been published (Evans et al. 2020). The BOI study is a retrospective and cross-sectional study, conducted in the UK. The study recruited a sample of N=24 neuromuscular specialists, who were surveyed between January 2020 and October 2020. Specialists were asked to complete a Case Record Form (CRF) for up to ten eligible patients capturing patient characteristics and direct health costs over the last 12 months. Eligible patients had a DMD diagnosis at least 24 months before the index date and carefully read, understood, and signed the informed consent form. Specialists then invited each patient to complete a corresponding Patient and Public Involvement and Engagement (PPIE) questionnaire. Dependent on the age of the patient, the PPIE form was completed by the patient (16 years or older), the patient's primary caregiver (4-7 years old), or a combination of both (8-16 years old). The PPIE provides direct and indirect non-medical cost information, including work loss and out-of-pocket expenses, as well as completion of validated patient reported outcomes measures, including the EQ-5D-5L, DMD-QoL and WPAI. The BOI study aimed to stratify results according to the eight health states published in the NHM.

The DMD-QoL is a University of Sheffield produced tool (created as part of Project HERCULES) which measures the HRQoL of patients with DMD, and dependent on age is completed by either the patient (self-complete) or the caregiver (proxy). This consists of 14 questions split into three domains: the physical domain, the social domain, and the physiological domain. These combine to produce a summary score.

The sample included n=197 patients. However, n=68 patients could not be stratified based on disease stage due to lack of relevant data. Therefore, n=129 patients contributed to the analyses. Of the n=129 patients, n=87 had a matched PPIE form (n=49 patient reported and n=38 caregiver reported). The average age across included patients was 14.18. The study obtained responses from the EQ-5D-Y (n=19), EQ-5D-5L (n=24), DMDQoL patient-reported (n=24), DMDQoL caregiver reported (n=16), and CarerQoL-7D (n=35) - Table 88.

The patient utility values derived from the self-reported EQ-5D-5L for patients ≥16-years varied from 0.52 to 0.66. The patient utility values derived from the self-reported DMD-QoL range from 0.33 to 0.54. For all measures explored in the BOI study, insufficient patient numbers were available to ascertain robust patient utility values by health state. Nevertheless, due to the case precedence of use of the BOI study in the ongoing NICE appraisal of vamorolone for treating DMD (GID-TA11135), the values derived from the self-reported DMD-QoL in this study are explored in a scenario analysis for patient utilities (NICE 2025).

Table 88: Patient utilities from Project HERCULES BOI study.

	EQ-5D-Y proxy-reported		EQ-5D-Y self-reported		EQ-5D-5L self-reported		DMD-QoL self-reported		DMD-QoL proxy-reported		CarerQoL	
Disease Stage	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Early ambulatory	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Late ambulatory	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Transfer	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HTMF, no ventilation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No HTMF, no ventilation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HTMF, night-time ventilation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No HTMF, night-time ventilation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Full time ventilation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Overall	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BOI, burden of illness; HTMF, hand to mouth function; NA, not available; SD, standard deviation.

Source: Evans et al. (2020)

Do et al. (2024) aimed to catalogue and compare existing published utilities for DMD with those reported for comparable conditions. Published utility estimates were identified using the Tufts CEA Registry, a comprehensive database of CEAs published from 1976 to the present. The CEA Registry focuses on a subset of cost-utility analyses that quantify health benefits in QALYs, which account for changes in both longevity and utility. At the time of this analysis, there were over 33,000 utility weights across more than 10,000 CEAs published from 1976 to 2021 within the registry. Eligible utility weight records included those derived from various countries, diseases, utility instruments, preference weights, and respondent types (i.e., proxy or self).

The first analysis consisted of identifying health states that have comparable HRQoL utility estimates with published US DMD utility estimates. A minimal clinically important difference of ± 0.03 was applied to each DMD utility estimate to establish a utility range. The registry was searched to identify other health states with associated utilities that fell within each range.

The second analysis consisted of identifying HRQoL utility estimates for health states that are similar to the clinical conditions of DMD. The registry was searched using pre-defined search terms, such as difficulty walking, joint and muscle weakness, loss of ambulation, and the use of a wheelchair. A clinical expert in DMD presentation next mapped each identified health state to five possible categories based on the degree of clinical similarity: early ambulatory (EA), late ambulatory (LA), early non-ambulatory (ENA), late non-ambulatory (LNA), and undetermined. Once the health state was mapped, the clinical expert gave a “relevancy score” on a scale of 0 to 10 based on how clinically similar the health state was to the DMD health state: score of 10, absolute relevance; score of < 10 to ≥ 8, substantial relevance; score of < 8 to ≥ 6, moderate relevance; <6 to ≥ 4, fair relevance; and < 4, slight-to-poor relevance. Health states were not specifically restricted to those plausible for a DMD model but had to reflect the signs and/or symptoms that would be relevant to DMD.

Analysis One identified 4,308 unique utilities across 2,322 cost-effectiveness publications (Do et al. 2024). The health states captured a wide range of acute and chronic conditions; 34% of utility records were extrapolated for US populations (n = 1,451); 1% were related to paediatric populations (n = 61). Analysis Two identified 153 utilities with health states clinically similar to DMD. The median utility estimates varied among identified health states. Health states similar to the early non-ambulatory DMD phase exhibited the greatest difference between the median estimate of the sample (0.39) and the existing estimate from published literature (0.21). results are presented in Table 89.

Overall, this study identified heterogeneity in health state utility estimates for conditions with similar utility estimates to existing DMD utilities as well as significant variability in utility estimates for health states clinically similar to DMD.

Table 89: Health states with comparable utility estimates to DMD from Do et al. 2024.

Criteria	DMD health state	Total utility records	Mean	Median	Std. Dev.	Interquartile Range
Analysis One						
All identified utility records	EA (0.70–0.76)	2,174	0.73	0.73	0.02	0.71–0.75
	LA (0.61–0.67)	1,841	0.64	0.65	0.02	0.63–0.66
	ENA (0.18–0.24)	223[a]	0.21	0.20	0.02	0.20–0.22
	LNA (0.15–0.21)	217[a]	0.19	0.19	0.02	0.17–0.20
Derived from US-based CEAs	EA	706	0.73	0.73	0.02	0.71–0.75
	LA	642	0.64	0.64	0.02	0.63–0.66
	ENA	86[b]	0.21	0.20	0.02	0.20–0.22
	LNA	79[b]	0.19	0.20	0.02	0.18–0.20
Pediatric populations	EA	37	0.73	0.73	0.02	0.72–0.75
	LA	14	0.64	0.64	0.02	0.62–0.65
	ENA	9[c]	0.20	0.20	0.007	0.20–0.20
	LNA	9[c]	0.20	0.20	0.02	0.20–0.20
Analysis Two						
10: absolute relevance (n=114)	EA	35	0.7	0.71	0.13	0.68–0.77
	LA	31	0.54	0.54	0.1	0.49–0.57
	ENA	39	0.37	0.39	0.17	0.29–0.46
	LNA	9	0.27	0.3	0.19	0.09–0.41
≥8: Absolute to substantial	EA	49	0.69	0.71	0.15	0.66–0.78
	LA	43	0.5	0.54	0.16	0.48–0.57

relevance (n=153)	ENA	46	0.32	0.39	0.19	0.21–0.46
	LNA	15	0.23	0.2	0.19	0.05–0.41

[a] 147 utility estimates were between 0.18–0.21 and included in both non-ambulatory phase datasets.

[b] 62 utility estimates were between 0.18–0.21 and included in both non-ambulatory phase datasets.

[c] 8 utility estimates were between 0.18–0.21 and included in both non-ambulatory phase datasets.

Abbreviations: CEA, cost-effectiveness analysis; DMD, Duchenne muscular dystrophy; EA, early ambulatory; ENA, early non-ambulatory; LA, late ambulatory; LNA, late non-ambulatory; US, United States.

Source: Do et al. (2024)

Appendix G. Probabilistic sensitivity analyses

An overview of PSA parameters is presented in Table 90.

Table 90: Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Population				
Average weight: Age 4	**	***	***	Normal
Average weight: Age 5	***	***	***	Normal
Average weight: Age 6	****	***	***	Normal
Average weight: Age 7	***	***	***	Normal
Average weight: Age 8	**	***	***	Normal
Average weight: Age 9	**	***	***	Normal
Average weight: Age 10	***	***	***	Normal
Average weight: Age 11	**	***	***	Normal
Average weight: Age 12	****	***	***	Normal
Average weight: Age 13	**	***	***	Normal
Average weight: Age 14	***	***	***	Normal
Average weight: Age 15	****	***	***	Normal
Average weight: Age 16	**	***	***	Normal
Average weight: Age 17	**	***	***	Normal
Average weight: Age 18	***	***	****	Normal
Average height: Age 4	***	***	****	Normal
Average height: Age 5	***	***	****	Normal
Average height: Age 6	****	****	****	Normal
Average height: Age 7	***	****	****	Normal
Average height: Age 8	***	****	****	Normal
Average height: Age 9	***	****	****	Normal
Average height: Age 10	***	****	****	Normal
Average height: Age 11	***	****	****	Normal
Average height: Age 12	***	****	****	Normal
Average height: Age 13	***	****	****	Normal
Average height: Age 14	***	****	****	Normal
Average height: Age 15	***	****	****	Normal
Average height: Age 16	***	****	****	Normal
Average height: Age 17	****	****	****	Normal
Average height: Age 18	****	****	****	Normal

NHM with transfer state, transition intensity state 1 to state 2	***	***	***	Log-normal
NHM with transfer state, transition intensity state 2 to state 4	***	***	***	Log-normal
NHM with transfer state, transition intensity state 4 to state 5	***	***	***	Log-normal
NHM with transfer state, transition intensity state 4 to state 6	***	***	***	Log-normal
NHM with transfer state, transition intensity state 5 to state 7a	***	***	***	Log-normal
NHM with transfer state, transition intensity state 7a to state 8a	***	***	***	Log-normal
NHM with transfer state, transition intensity state 6 to state 7b	***	***	***	Log-normal
Natural history model with transfer state, transition intensity state 7b to state 8b	***	***	***	Log-normal
Original NHM: To state 2 - Late ambulatory	*	**	**	Log-normal
Original NHM: To state 3 - Transfer	*	**	**	Log-normal
Original NHM: To state 4 - HTMF, no ventilation	*	**	**	Log-normal
Original NHM: To state 5 - No HTMF, no ventilation	*	**	**	Log-normal
Original NHM: To state 7a - No HTMF, night-time ventilation	*	**	**	Log-normal
Original NHM: To state 8a - Full time ventilation	*	**	**	Log-normal
Original NHM: To state 6 - HTMF, night-time ventilation	*	**	**	Log-normal
Original NHM: To state 7b - No HTMF, night-time ventilation	*	**	**	Log-normal
Original NHM: To state 8b - Full time ventilation	*	**	**	Log-normal
Original NHM: From state 1 - Early ambulatory	*	**	**	Log-normal
Original NHM: From state 2 - Late ambulatory	*	**	**	Log-normal

Original NHM: From state 3 - Transfer	*	**	**	Log-normal
Original NHM: From state 4 - HTMF, no ventilation	*	**	**	Log-normal
Original NHM: From state 5 - No HTMF, no ventilation	*	**	**	Log-normal
Original NHM: From state 7a - No HTMF, night-time ventilation	*	**	**	Log-normal
Original NHM: From state 8a - Full time ventilation	*	**	**	Log-normal
Original NHM: From state 6 - HTMF, night-time ventilation	*	**	**	Log-normal
Original NHM: From state 7b - No HTMF, night-time ventilation	*	**	**	Log-normal
Original NHM: From state 8b - Full time ventilation	*	**	**	Log-normal
Health states 2-4 and 8a-8b NHM: To state 2 - Late ambulatory	***	**	**	Log-normal
Health states 2-4 and 8a-8b NHM: To state 3 - Transfer	***	**	**	Log-normal
Health states 2-4 and 8a-8b NHM: To state 4 - HTMF, no ventilation	***	**	**	Log-normal
Health states 2-4 and 8a-8b NHM: To state 5 - No HTMF, no ventilation	*	**	**	Log-normal
Health states 2-4 and 8a-8b NHM: To state 7a - No HTMF, night-time ventilation	*	**	**	Log-normal
Health states 2-4 and 8a-8b NHM: To state 8a - Full time ventilation	*	**	**	Log-normal
Health states 2-4 and 8a-8b NHM: To state 6 - HTMF, night-time ventilation	*	**	**	Log-normal
Health states 2-4 and 8a-8b NHM: To state 7b - No HTMF, night-time ventilation	*	**	**	Log-normal
Health states 2-4 and 8a-8b NHM: To state 8b - Full time ventilation	*	**	**	Log-normal
Health states 2-4 and 8a-8b NHM: From state 1 - Early ambulatory	*	**	**	Log-normal

Health states 2-4 and 8a-8b NHM: From state 2 - Late ambulatory	*	**	**	Log-normal
Health states 2-4 and 8a-8b NHM: From state 3 - Transfer	*	**	**	Log-normal
Health states 2-4 and 8a-8b NHM: From state 4 - HTMF, no ventilation	*	**	**	Log-normal
Health states 2-4 and 8a-8b NHM: From state 5 - No HTMF, no ventilation	*	**	**	Log-normal
Health states 2-4 and 8a-8b NHM: From state 7a - No HTMF, night-time ventilation	*	**	**	Log-normal
Health states 2-4 and 8a-8b NHM: From state 8a - Full time ventilation	***	**	**	Log-normal
Health states 2-4 and 8a-8b NHM: From state 6 - HTMF, night-time ventilation	*	**	**	Log-normal
Health states 2-4 and 8a-8b NHM: From state 7b - No HTMF, night-time ventilation	*	**	**	Log-normal
Health states 2-4 and 8a-8b NHM: From state 8b - Full time ventilation	***	**	**	Log-normal
Health states 8a-8b NHM: To state 2 - Late ambulatory	*	**	**	Log-normal
Health states 8a-8b NHM: To state 3 - Transfer	*	**	**	Log-normal
Health states 8a-8b NHM: To state 4 - HTMF, no ventilation	*	**	**	Log-normal
Health states 8a-8b NHM: To state 5 - No HTMF, no ventilation	*	**	**	Log-normal
Health states 8a-8b NHM: To state 7a - No HTMF, night-time ventilation	*	**	**	Log-normal
Health states 8a-8b NHM: To state 8a - Full time ventilation	*	**	**	Log-normal
Health states 8a-8b NHM: To state 6 - HTMF, night-time ventilation	*	**	**	Log-normal
Health states 8a-8b NHM: To state 7b - No HTMF, night-time ventilation	*	**	**	Log-normal

Health states 8a-8b NHM: To state 8b - Full time ventilation	*	**	**	Log-normal
Health states 8a-8b NHM: From state 1 - Early ambulatory	*	**	**	Log-normal
Health states 8a-8b NHM: From state 2 - Late ambulatory	*	**	**	Log-normal
Health states 8a-8b NHM: From state 3 - Transfer	*	**	**	Log-normal
Health states 8a-8b NHM: From state 4 - HTMF, no ventilation	*	**	**	Log-normal
Health states 8a-8b NHM: From state 5 - No HTMF, no ventilation	*	**	**	Log-normal
Health states 8a-8b NHM: From state 7a - No HTMF, night-time ventilation	*	**	**	Log-normal
Health states 8a-8b NHM: From state 8a - Full time ventilation	**	**	**	Log-normal
Health states 8a-8b NHM: From state 6 - HTMF, night-time ventilation	*	**	**	Log-normal
Health states 8a-8b NHM: From state 7b - No HTMF, night-time ventilation	*	**	**	Log-normal
Health states 8a-8b NHM: From state 8b - Full time ventilation	**	**	**	Log-normal
Duvyzat® (givinostat) hazard ratio: To state 2 - Late ambulatory	***	***	***	Log-normal
Duvyzat® (givinostat) hazard ratio: To state 4 - HTMF, no ventilation	***	***	***	Log-normal
Duvyzat® (givinostat) hazard ratio: Not in Use	***	***	***	Log-normal
Duvyzat® (givinostat) hazard ratio: To state 5 - No HTMF, no ventilation	***	***	***	Log-normal
Duvyzat® (givinostat) hazard ratio: To state 7a - No HTMF, night-time ventilation	***	***	***	Log-normal
Duvyzat® (givinostat) hazard ratio: To state 8a - Full time ventilation	***	***	***	Log-normal

Duvyzat® (givinostat) hazard ratio: To state 6 - HTMF, night-time ventilation	***	***	***	Log-normal
Duvyzat® (givinostat) hazard ratio: To state 7b - No HTMF, night-time ventilation	***	***	***	Log-normal
Duvyzat® (givinostat) hazard ratio: To state 8b - Full time ventilation	***	***	***	Log-normal
Duvyzat® (givinostat) - Decreased platelet count - EPIDYS	**	***	***	Normal
Duvyzat® (givinostat) - Thrombocytopenia - EPIDYS	**	***	***	Normal
Duvyzat® (givinostat) - Increased blood triglyceride concentration - EPIDYS	**	***	***	Normal
Duvyzat® (givinostat) - Hyperglyceridaemia - EPIDYS	**	***	***	Normal
Duvyzat® (givinostat) - Diarrhoea - EPIDYS	**	***	***	Normal
Duvyzat® (givinostat) - Abdominal pain - EPIDYS	**	***	***	Normal
Duvyzat® (givinostat) - Upper abdominal pain - EPIDYS	*	**	***	Normal
Duvyzat® (givinostat) - Vomiting - EPIDYS	*	**	***	Normal
Duvyzat® (givinostat) - Decreased platelet count - Study 51	**	***	***	Normal
Duvyzat® (givinostat) - Thrombocytopenia - Study 51	**	***	***	Normal
Duvyzat® (givinostat) - Increased blood triglyceride concentration - Study 51	**	***	***	Normal
Duvyzat® (givinostat) - Hyperglyceridaemia - Study 51	**	***	***	Normal
Duvyzat® (givinostat) - Diarrhoea - Study 51	**	***	***	Normal
Duvyzat® (givinostat) - Abdominal pain - Study 51	**	***	***	Normal
Duvyzat® (givinostat) - Upper abdominal pain - Study 51	*	**	**	Normal
Duvyzat® (givinostat) - Vomiting - Study 51	*	**	**	Normal
Clinical management without givinostat -	*	**	**	Normal

Decreased platelet count - EPIDYS				
Clinical management without givinostat - Thrombocytopenia - EPIDYS	*	**	**	Normal
Clinical management without givinostat - Increased blood triglyceride concentration - EPIDYS	*	**	**	Normal
Clinical management without givinostat - Hyperglyceridaemia - EPIDYS	*	**	**	Normal
Clinical management without givinostat - Diarrhoea - EPIDYS	*	**	**	Normal
Clinical management without givinostat - Abdominal pain - EPIDYS	*	**	**	Normal
Clinical management without givinostat - Upper abdominal pain - EPIDYS	*	**	**	Normal
Clinical management without givinostat - Vomiting - EPIDYS	*	**	**	Normal
Duvyzat® (givinostat): Time to surgery after loss of ambulation (years)	*	**	**	Log-normal
Clinical management without givinostat % pts receiving spinal surgery	****	**	**	Beta
Clinical management without givinostat: Time to surgery after loss of ambulation (years)	*	**	**	Log-normal
Number of patients discontinued givinostat - EPIDYS	*	**	**	Normal
Number of patients discontinued givinostat - Study 51	*	**	**	Normal
Number of patients discontinued SOC - EPIDYS	*	**	**	Normal
Givinostat compliance - EPIDYS	*****	**	**	Beta
Givinostat compliance - Study 51	*****	**	**	Beta
SOC compliance - SOC	*****	**	**	Beta
Givinostat number with dose modifications - EPIDYS	**	***	****	Normal

Givinostat number with dose reductions - EPIDYS	**	***	***	Normal
Givinostat number with dose temporarily stopped - EPIDYS	**	***	***	Normal
Givinostat number with dose skipped - EPIDYS	**	***	***	Normal
Givinostat number with dose increased - EPIDYS	**	**	**	Normal
Givinostat number with dose permanently stopped - EPIDYS	**	**	***	Normal
Givinostat number with dose modifications - Study 51	***	***	****	Normal
Givinostat number with dose reductions - Study 51	**	***	***	Normal
Givinostat number with dose temporarily stopped - Study 51	**	***	***	Normal
Givinostat number with dose skipped - Study 51	**	***	***	Normal
Givinostat number with dose increased - Study 51	**	***	***	Normal
Givinostat number with dose permanently stopped - Study 51	**	***	***	Normal
SOC number with dose modifications - EPIDYS	**	***	***	Normal
SOC number with dose reductions - EPIDYS	*	**	**	Normal
SOC number with dose temporarily stopped - EPIDYS	*	**	**	Normal
SOC number with dose skipped - EPIDYS	**	***	***	Normal
SOC number with dose increased - EPIDYS	*	**	**	Normal
SOC number with dose permanently stopped - EPIDYS	*	**	**	Normal
Patient utilities: Audhya et al. (2023) - 1 - Early ambulatory	***	**	**	Beta
Patient utilities: Audhya et al. (2023) - 2 - Late ambulatory	***	**	**	Beta
Patient utilities: Audhya et al. (2023) - 3 - Transfer	***	**	**	Beta

Patient utilities: Audhya et al. (2023) - 4 - HTMF, no ventilation	****	**	**	Beta
Patient utilities: Audhya et al. (2023) - 5 - No HTMF, no ventilation	****	**	**	Beta
Patient utilities: Audhya et al. (2023) - 6 - HTMF, night-time ventilation	****	**	**	Beta
Patient utilities: Audhya et al. (2023) - 7 - No HTMF, night-time ventilation	****	**	**	Beta
Patient utilities: Audhya et al. (2023) - 8 - Full time ventilation	****	**	**	Beta
Spinal fusion surgery: Disutility	***	**	**	Beta
Spinal fusion surgery: Duration of disutility (years)	*	**	**	Normal
Decreased platelet count: Disutilities	*	**	**	Beta
Thrombocytopenia: Disutilities	*	**	**	Beta
Increased blood triglyceride concentration: Disutilities	*	**	**	Beta
Hyperglyceridaemia: Disutilities	*	**	**	Beta
Diarrhoea: Disutilities	****	**	**	Beta
Abdominal pain: Disutilities	****	**	**	Beta
Upper abdominal pain: Disutilities	****	**	**	Beta
Vomiting: Disutilities	****	**	**	Beta
Decreased platelet count: Duration of event (days)	*	**	**	Normal
Increased blood triglyceride concentration: Duration of event (days)	*	**	**	Normal
Diarrhoea: Duration of event (days)	**	**	**	Normal
Abdominal pain: Duration of event (days)	**	**	**	Normal
Upper abdominal pain: Duration of event (days)	**	**	**	Normal
Vomiting: Duration of event (days)	**	**	**	Normal
Price / pack (NOK) - Prednisone	****	***	***	Gamma

Price / pack (NOK) - Deflazacort	***	*****	******	Gamma
Spinal fusion surgery - Cost per unit (NOK) - Spinal surgery cost	********	********	*********	Gamma
Spinal fusion surgery - Cost per unit (NOK) - Surgery follow-up	*******	*******	*******	Gamma
Spinal fusion surgery - Units per patient - Spinal surgery cost	*	**	**	Normal
Spinal fusion surgery - Units per patient - Surgery follow-up	*	**	**	Normal
Direct medical costs by health state (Landfeldt) - 1 - Early ambulatory	*****	******	******	Gamma
Direct medical by health state (Landfeldt) - 2 - Late ambulatory	*****	******	******	Gamma
Direct medical by health state (Landfeldt) - 4 - HTMF, no ventilation	*****	******	******	Gamma
Direct medical by health state (Landfeldt) - 5 - No HTMF, no ventilation	*****	******	******	Gamma
Direct medical by health state (Landfeldt) - 6 - HTMF, night-time ventilation	*****	******	******	Gamma
Direct medical by health state (Landfeldt) - 7 - No HTMF, night-time ventilation	*****	******	******	Gamma
Direct medical by health state (Landfeldt) - 8 - Full time ventilation	*****	******	******	Gamma

Appendix H. Literature searches for the clinical assessment

Efficacy and safety of the intervention and comparator(s)

Identification and selection of relevant studies

An SLR was conducted to identify all published evidence of the clinical efficacy, safety and tolerability of givinostat and established clinical management (ECM) for DMD.

A comprehensive literature search was conducted following the standards set out in the PRISMA and Cochrane Handbook for Systematic Reviews of Interventions guidelines, as well as the rigorous standards required by NICE and most other agencies. The search strategy included a combination of medical subject headings (MeSH) or Emtree terms in addition to free-text terms for articles on human subjects published in English. A set of detailed search strings along with the number of hits retrieved are listed in Table 94. The searches were originally performed on 08 May 2024 for databases and 09–13 May 2024 for congresses and health technology assessment (HTA) bodies. Further searches on any other sources were conducted on 10 June 2024. An update of the SLR was run in November 2024, with database searches on the 07–08 November, and hand searches on 06 November.

Search strategy | electronic databases and hand searches

In Table 91, the databases searched are listed.

Table 91: Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	embase.com	• Full publication: No time limit • Conference abstract: May 2022 to present	08.11.2024
Medline	pubmed.com	• Full publication: No time limit	08.11.2024

Database	Platform/source	Relevant period for the search	Date of search completion
		• Conference abstract: May 2022 to present	
CENTRAL	wiley.com	• Full publication: No time limit • Conference abstract: May 2022 to present	08.11.2024

Searches were designed to identify relevant RCTs, as well as sources of real-world data relevant to the decision problem. In particular, search strings and screening criteria were developed to identify the most appropriate data sources on natural history outcomes with ECM for patients with DMD in the UK. Non-UK real-world data sources were explored in the original SLR, while the update focused on UK real-world data sources only. Further details of the selection criteria relating to the real-world data used in the indirect treatment comparisons and economic model are presented in Section 0.

The search strings used to identify relevant studies for the original SLR are provided in Section 0. The search strings for the SLR update are provided in Section 0.

Hand searching supplemented the electronic database searches. The sources examined are described below.

Table 92: Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
National Institute for Health and Care Excellence	https://www.nice.org.uk/	See table note a	6.11.2024
Scottish Medicines Consortium	https://scottishmedicines.org.uk/	See table note a	6.11.2024
National Centre for Pharmacoeconomics, Ireland	https://www.ncpe.ie/	See table note a	6.11.2024
Institute for Clinical and Economic Review	https://icer.org/	See table note a	6.11.2024

Source name	Location/source	Search strategy	Date of search
European Union net Health Technology Agency	https://www.ema.europa.eu/en/partners-networks/health-technology-assessment-bodies	See table note a	6.11.2024
Canada's Drug and Health Technology Agency	https://www.cda-amc.ca/	See table note a	6.11.2024
The Pharmaceutical Benefits Advisory Committee	https://www.pbs.gov.au/info/industry/listing/participants/pbac	See table note a	6.11.2024
Therapeutics Goods Administration	https://www.tga.gov.au/	See table note a	6.11.2024

Notes: a: Firstly, published SLRs and network meta-analyses (NMAs) that were identified in database searches were reviewed to identify relevant primary publications. Secondly, to identify further studies not captured in the electronic database searches, proceedings of relevant congresses held between 2022–2024 (inclusive) were searched via the conferences' online platforms or via downloadable abstract books. Finally, HTA bodies were reviewed to identify evidence from the last 10 years not captured in the electronic database searches. Hand searches were repeated between the 06 and 08 November for the updated review.

Table 93: Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
Annual Congress of the World Muscle Society	https://www.worldmusclesociety.org/	See table note a	Duchenne muscular dystrophy	6.11.2024
International Congress of Neuropathology	https://www.intsocneuropathol.com/	See table note a	Duchenne muscular dystrophy	6.11.2024
Action Duchenne Annual International Conference, linked with the DMD registry part of the TREAT-NMD	https://www.actionduchenne.org/	See table note a	Duchenne muscular dystrophy	6.11.2024

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
Global Registries				
TREAT-NMD International Conference	https://www.treat-nmd.org/	See table note a	Duchenne muscular dystrophy	6.11.2024
International Pediatric Summit	https://leqaauae.com/	See table note a	Duchenne muscular dystrophy	6.11.2024
Muscular dystrophy association (MDA) conference	https://www.mdaconference.org/	See table note a	Duchenne muscular dystrophy	6.11.2024
British Paediatric Neurology Association Annual Conference	e.g. conference website	See table note a	Duchenne muscular dystrophy	6.11.2024
Myology Congress	https://www.myology2024.org/	See table note a	Duchenne muscular dystrophy	6.11.2024
Congress of the European Paediatric Neurology Society (EPNS)	https://www.epns.info/	See table note a	Duchenne muscular dystrophy	6.11.2024

Notes: a: Firstly, published SLRs and network meta-analyses (NMAs) that were identified in database searches were reviewed to identify relevant primary publications. Secondly, to identify further studies not captured in the electronic database searches, proceedings of relevant congresses held between 2022–2024 (inclusive) were searched via the conferences' online platforms or via downloadable abstract books. Finally, HTA bodies were reviewed to identify evidence from the last 10 years not captured in the electronic database searches. Hand searches were repeated between the 06 and 08 November for the updated review.

In addition, the following sources were searched for relevant data from the last 10 years to identify linked publications, and additional studies not identified in the electronic database searches, congress searches or HTA searches:

- Government/international bodies (NIHR Innovation Observatory, NIHR UK Journals Library, Agency for Healthcare Research and Quality, EMA)
- Additional sources (ClinicalTrials.gov, International Clinical Trials Registry Platform [ICTRP], European Union Clinical Trials Register)

Search strategies

Original SLR review May 2024

The search strings used to identify relevant studies are provided in Table 94 for MEDLINE®, Table 95 for Embase® and Table 96 for Cochrane.

Table 94: Search strategy for MEDLINE® via PubMed® (original search)

No.	Query	Results
#1	Disease string ("Muscular Dystrophy, Duchenne"[MeSH] OR (("Duchenne"[Title/Abstract] AND ("dystrophy"[Title/Abstract] OR "morbus"[Title/Abstract] OR "syndrome"[Title/Abstract] OR "muscular"[Title/Abstract])) OR "DMD"[Title/Abstract]) NOT ("becker"[Title/Abstract] OR "Duchenne becker"[Title/Abstract])	15,433
#2	Givinostat "givinostat"[Title/Abstract] OR "ITF2357"[Title/Abstract] OR "ITF 2357"[Title/Abstract] OR "ITF-2357"[Title/Abstract]	152
#3	Ataluren "ataluren"[Title/Abstract] OR "translarna"[Title/Abstract] OR "PTC124"[Title/Abstract] OR "PTC 124"[Title/Abstract] OR "PTC-124"[Title/Abstract]	266
#4	Delandistrogene moxeparvovec "delandistrogene"[Title/Abstract] OR "delandistrogene moxeparvovec"[Title/Abstract] OR "elevidys"[Title/Abstract] OR "SRP-9001"[Title/Abstract] OR "SRP 9001"[Title/Abstract] OR "SRP9001"[Title/Abstract]	12
#5	Fordadistrogene movaparvovec "fordadistrogene"[Title/Abstract] OR "fordadistrogene movaparvovec"[Title/Abstract] OR "PF-06939926"[Title/Abstract] OR "PF 06939926"[Title/Abstract] OR "PF06939926"[Title/Abstract]	1
#6	#2 OR #3 OR #4 OR #5	430
#7	Adrenal cortex hormones "adrenal cortex hormones"[MeSH Terms] OR "Prednisolone"[MeSH Terms] OR "corticosteroid*"[Title/Abstract] OR "glucocorticoid*"[Title/Abstract] OR "prednisone"[Title/Abstract] OR "deflazacort"[Title/Abstract] or "steroid*"[Title/Abstract]	685,318
#8	ACE or ARB inhibitors "angiotensin converting enzyme inhibitors"[MeSH Terms] OR "lisinopril"[MeSH Terms] OR "perindopril"[MeSH Terms] OR "ramipril"[MeSH Terms] OR "ACE inhibitors"[Title/Abstract] OR	63,779

	"lisinopril"[Title/Abstract] OR "perindopril"[Title/Abstract] OR "ramipril"[Title/Abstract] OR "angiotensin receptor antagonists"[MeSH Terms] OR "irbesartan"[MeSH Terms] OR "candesartan"[Supplementary concept] OR "losartan"[MeSH Terms] OR "angiotensin receptor antagonists"[Title/Abstract] OR "irbesartan"[Title/Abstract] OR "candesartan" [Title/Abstract] OR "losartan"[Title/Abstract]	
#9	Beta blockers	36,419
	"beta blockers"[Title/Abstract] OR "adrenergic beta-antagonists"[MeSH Terms] OR "bisoprolol"[MeSH Terms] "metoprolol"[MeSH Terms] "bisoprolol"[Title/Abstract] "metoprolol"[Title/Abstract] OR "beta blocker*"[Title/Abstract] OR "beta antagonist*"[Title/Abstract] OR "beta-blocker*"[Title/Abstract] OR "beta-antagonist*"[Title/Abstract]	
#10	Heart function preservation	33,175
	"ivabradine"[MeSH Terms] OR "Mineralocorticoids"[MeSH Terms] OR "eplerenone"[MeSH Terms] OR "spironolactone"[MeSH Terms] OR "ivabradine"[Title/Abstract] OR "Mineralocorticoid*"[Title/Abstract] OR "MRA"[Title/Abstract] OR (("MRA"[Title/Abstract] OR "mineralocorticoid*"[Title/Abstract]) AND ("blocking drug*"[Title/Abstract] OR "blocking-drug*"[Title/Abstract])) OR "eplerenone"[Title/Abstract] OR "spironolactone"[Title/Abstract]	
#11	Neuropsychological therapy	15,650
	Neuropsycholog*[Title/Abstract] AND ("therap*"[Title/Abstract] OR "treatment"[Title/Abstract])	
#12	Occupational therapy	40,568
	(("Occupational"[Title/Abstract]) AND ("therap*"[Title/Abstract] OR "treatment"[Title/Abstract])) OR "Occupational Therapy"[MeSH Terms]	
#13	Physiotherapy	225,198
	Physiotherap*[Title/Abstract] OR "Physical Therapy Modalities"[MeSH Terms] OR "physical therap*"[Title/Abstract] OR "HTMF"[Title/Abstract]	
#14	Pacemaker	54,113
	"pacemaker, artificial"[MeSH Terms] OR ("pacemaker"[Title/Abstract] AND "artificial"[Title/Abstract]) OR "pacemaker"[Title/Abstract] OR "artificial cardiac pacemaker"[Title/Abstract] OR (("pacemaker"[Title/Abstract]) AND ("artificial"[Title/Abstract] OR "cardiac"[Title/Abstract]))	
#15	Surgery	20,866
	"spine surger*"[Title/Abstract] OR "spinal surger*"[Title/Abstract]	
#16	Ventilation	198,720

	"Respiration, Artificial"[MeSH Terms] OR "Ventilation"[Title/Abstract] OR "artificial respiration"[Title/Abstract]	
#17	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16	1,320,457
#18	Publication type: RCTs "Randomized Controlled Trials as Topic"[MeSH Terms] OR "Clinical Trials as Topic"[MeSH Terms] OR "random allocation"[MeSH Terms] OR "Double-Blind Method"[MeSH Terms] OR "Single-Blind Method"[MeSH Terms] OR "placebo effect"[MeSH Terms] OR "placebos"[MeSH Terms] OR "control groups"[MeSH Terms] OR "cross-over studies"[MeSH Terms] OR "Controlled Clinical Trial"[Publication Type] OR "Clinical Trial, Phase II"[Publication Type] OR "Clinical Trial, Phase III"[Publication Type] OR "Clinical Trial, Phase IV"[Publication Type] OR "RCT"[Title/Abstract] OR "randomisation"[Title/Abstract] OR "randomization"[Title/Abstract] OR "randomised controlled trial"[Title/Abstract] OR "randomized controlled trial"[Title/Abstract] OR (("random*"[Title/Abstract]) AND ("trial"[Title/Abstract] OR "control*"[Title/Abstract] OR "assign*"[Title/Abstract] OR "allocat*"[Title/Abstract] OR "stud*"[Title/Abstract] OR "clinical"[Title/Abstract])) OR (("placeb*"[Title/Abstract]) AND ("trial"[Title/Abstract] OR "control*"[Title/Abstract] OR "assign*"[Title/Abstract] OR "allocat*"[Title/Abstract] OR "stud*"[Title/Abstract] OR "clinical"[Title/Abstract])) OR (("control*"[Title/Abstract]) AND ("clinical"[Title/Abstract] OR "trial"[Title/Abstract] OR "group"[Title/Abstract])) OR "control group"[Title/Abstract] OR (("single"[Title/Abstract] OR "double"[Title/Abstract] OR "triple"[Title/Abstract] OR "treble"[Title/Abstract]) AND ("blind"[Title/Abstract] OR "blind*"[Title/Abstract] OR "mask"[Title/Abstract] OR "mask*"[Title/Abstract])) OR "open label"[Title/Abstract] OR "open-label"[Title/Abstract] OR "clinical study"[Title/Abstract] OR "clinical article"[Title/Abstract]	3,248,032
#19	Publication type: single-arm trials "single arm"[Title/Abstract] OR "single-arm"[Title/Abstract] OR (("single arm"[Title/Abstract] OR "single-arm"[Title/Abstract]) AND ("trial*"[Title/Abstract] OR "stud*"[Title/Abstract]))	14,898
#20	Publication type: real-world or observational studies "Case-Control Studies"[MeSH Terms] OR "clinical audit"[MeSH Terms] OR "comparative study"[Publication Type] OR "observational study"[Publication Type] OR (("comparat*"[Title/Abstract]) AND ("trial"[Title/Abstract] OR "stud*"[Title/Abstract])) OR (("epidemiologic*"[Title/Abstract] OR "case-control"[Title/Abstract] OR "case control"[Title/Abstract] OR "cross-section*"[Title/Abstract] OR "cross section*"[Title/Abstract] OR "cohort"[Title/Abstract] OR "retrospectiv*"[Title/Abstract] OR "longitudinal"[Title/Abstract] OR "prospective"[Title/Abstract] OR "observation*"[Title/Abstract] OR "comparative"[Title/Abstract] OR "follow-up"[Title/Abstract] OR "follow up"[Title/Abstract] OR "crossover"[Title/Abstract] OR "cross-over"[Title/Abstract] OR "non-	6,663,938

	randomised”[Title/Abstract] OR “non-randomized”[Title/Abstract]) AND (“stud*”[Title/Abstract] OR “trial*”[Title/Abstract] OR “analys*”[Title/Abstract] or “procedure”[Title/Abstract])) OR “Pragmatic Clinical Trial”[Title/Abstract] OR ((“hospital”[Title/Abstract] OR “medical”[Title/Abstract] OR “electronic”[Title/Abstract]) AND (“record*”[Title/Abstract] OR “chart*”[Title/Abstract])) OR “registry”[Title/Abstract] OR “non random”[Title/Abstract] OR “single arm”[Title/Abstract] OR “real world”[Title/Abstract] OR “real life”[Title/Abstract] OR “real world”[Title/Abstract] OR “northstar”[Title/Abstract] OR “north star”[Title/Abstract]	
#21	#18 OR #19 OR #20	8,538,924
#22	Publication Type: Not required publications (e.g. Comment, Letter, Editorial, Case Reports, Guideline etc.) “case reports”[Publication Type] OR “editorial”[Publication Type] OR “letter”[Publication Type] OR “comment”[Publication Type] OR “clinical trial, veterinary”[Publication Type] OR “Guideline”[Publication Type] OR “News”[Publication Type] OR “Lecture”[Publication Type] OR “Interview”[Publication Type]	4,699,889
#23	Publication Type: Not required publications (e.g. animal studies) “animals”[MeSH Terms] NOT (“animals”[MeSH Terms] AND “humans”[MeSH Terms])	5,218,121
#24	#22 OR #23	9,786,681
#25	#21 NOT #24	7,280,504
#26	#1 AND #6 AND #25	52
#27	#1 AND #17 AND #25	758
#28	#26 OR #27	787

Table 95: Search strategy for Embase® via embase.com (original search)

No.	Query	Results
#1	Disease string ('Duchenne muscular dystrophy'/syn OR ('duchenne':ti,ab,kw AND ('dystrophy':ti,ab,kw OR 'morbus':ti,ab,kw OR 'syndrome':ti,ab,kw OR 'muscular':ti,ab,kw)) OR 'dmd':ti,ab,kw) NOT ('becker':ti,ab,kw OR 'duchenne becker':ti,ab,kw)	25,357
#2	Givinostat	275

	'givinostat':ti,ab,kw OR 'itf2357':ti,ab,kw OR 'itf 2357':ti,ab,kw OR 'itf-2357':ti,ab,kw	
#3	Ataluren 'ataluren':ti,ab,kw OR 'translarna':ti,ab,kw OR 'ptc124':ti,ab,kw OR 'ptc 124':ti,ab,kw OR 'ptc-124':ti,ab,kw	651
#4	Delandistrogene moxeparvovec 'delandistrogene':ti,ab,kw OR 'delandistrogene moxeparvovec':ti,ab,kw OR 'elevidys':ti,ab,kw OR 'srp-9001':ti,ab,kw OR 'srp 9001':ti,ab,kw OR 'srp9001':ti,ab,kw	55
#5	Fordadistrogene movaparvovec 'fordadistrogene':ti,ab,kw OR 'fordadistrogene movaparvovec':ti,ab,kw OR 'pf-06939926':ti,ab,kw OR 'pf 06939926':ti,ab,kw OR 'pf06939926':ti,ab,kw	5
#6	#2 OR #3 OR ‘4 OR #5	986
#7	Adrenal cortex hormones 'corticosteroid'/exp OR 'prednisolone'/exp OR 'corticosteroid*':ti,ab,kw OR 'glucocorticoid*':ti,ab,kw OR 'prednisone':ti,ab,kw OR 'deflazacort':ti,ab,kw OR 'prednisolone':ti,ab,kw OR 'steroid*':ti,ab,kw	1,556,857
#8	ACE inhibitors 'dipeptidyl carboxypeptidase inhibitor'/exp OR 'lisinopril'/exp OR 'perindopril'/exp OR 'ramipril'/exp OR 'ace inhibitor*':ti,ab,kw OR 'lisinopril':ti,ab,kw OR 'perindopril':ti,ab,kw OR 'ramipril':ti,ab,kw OR 'angiotensin receptor antagonist'/exp OR 'irbesartan'/exp OR 'losartan'/exp OR 'angiotensin receptor antagonist*':ti,ab,kw OR 'irbesartan':ti,ab,kw OR 'candesartan':ti,ab,kw OR 'losartan':ti,ab,kw	268,342
#9	Beta blockers 'beta blockers':ti,ab,kw OR 'beta adrenergic receptor blocking agent'/exp OR 'bisoprolol'/exp OR 'metoprolol'/exp OR 'bisoprolol':ti,ab,kw OR 'metoprolol':ti,ab,kw OR 'beta blocker*':ti,ab,kw OR 'beta antagonist*':ti,ab,kw OR 'beta-blocker*':ti,ab,kw OR 'beta-antagonist*':ti,ab,kw	360,355
#10	Heart function preservation 'ivabradine'/exp OR 'mineralocorticoid'/exp OR 'eplerenone'/exp OR 'spironolactone'/exp OR 'ivabradine':ti,ab,kw OR 'mineralocorticoid*':ti,ab,kw OR 'mra':ti,ab,kw OR (('mra':ti,ab,kw OR 'mineralocorticoid*':ti,ab,kw) AND ('blocking drug*':ti,ab,kw OR 'blocking-drug*':ti,ab,kw)) OR 'eplerenone':ti,ab,kw OR 'spironolactone':ti,ab,kw	168,730

#11	Neuropsychological therapy 'neuropsycholog*':ti,ab,kw AND ('therap*':ti,ab,kw OR 'treatment':ti,ab,kw)	26,228
#12	Occupational therapy (('occupational':ti,ab,kw) AND ('therap*':ti,ab,kw OR 'treatment':ti,ab,kw)) OR 'occupational therapy'/exp	64,570
#13	Physiotherapy 'physiotherap*':ti,ab,kw OR 'physiotherapy'/exp OR 'physical therap*':ti,ab,kw OR 'HTMF':ti,ab,kw	167,243
#14	Pacemaker 'artificial heart pacemaker'/exp OR ('pacemaker':ti,ab,kw AND 'artificial':ti,ab,kw) OR 'pacemaker':ti,ab,kw OR 'artificial cardiac pacemaker':ti,ab,kw OR ('pacemaker':ti,ab,kw AND ('artificial':ti,ab,kw OR 'cardiac':ti,ab,kw))	85,131
#15	Surgery 'spine surger*':ti,ab,kw OR 'spinal surger*':ti,ab,kw	27,574
#16	Ventilation 'artificial ventilation'/exp OR 'ventilation':ti,ab,kw OR 'artificial respiration':ti,ab,kw	400,422
#17	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16	2,731,268
#18	Publication type: RCTs 'randomized controlled trial (topic)'/exp OR 'clinical trial (topic)'/exp OR 'randomization'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR 'placebo effect'/exp OR 'placebo'/exp OR 'control group'/exp OR 'crossover procedure'/exp OR 'controlled clinical trial':it OR 'clinical trial, phase ii':it OR 'clinical trial, phase iii':it OR 'clinical trial, phase iv':it OR 'rct':ti,ab,kw OR 'randomisation':ti,ab,kw OR 'randomization':ti,ab,kw OR 'randomised controlled trial':ti,ab,kw OR 'randomized controlled trial':ti,ab,kw OR (('random*':ti,ab,kw) AND ('trial':ti,ab,kw OR 'control*':ti,ab,kw OR 'assign*':ti,ab,kw OR 'allocat*':ti,ab,kw OR 'stud*':ti,ab,kw OR 'clinical':ti,ab,kw)) OR (('placeb*':ti,ab,kw) AND ('trial':ti,ab,kw OR 'control*':ti,ab,kw OR 'assign*':ti,ab,kw OR 'allocat*':ti,ab,kw OR 'stud*':ti,ab,kw OR 'clinical':ti,ab,kw)) OR (('control*':ti,ab,kw) AND ('clinical':ti,ab,kw OR 'trial':ti,ab,kw OR 'group':ti,ab,kw)) OR 'control group':ti,ab,kw OR (('single':ti,ab,kw OR 'double':ti,ab,kw OR 'triple':ti,ab,kw OR 'treble':ti,ab,kw) AND ('blind':ti,ab,kw OR 'blind*':ti,ab,kw OR 'mask':ti,ab,kw OR 'mask*':ti,ab,kw)) OR 'open label':ti,ab,kw OR 'open-label':ti,ab,kw OR 'clinical study':ti,ab,kw OR 'clinical article':ti,ab,kw	4,508,674
#19	Publication type: single-arm trials	31,073

	'single arm':ti,ab,kw OR 'single-arm':ti,ab,kw OR (('single arm':ti,ab,kw OR 'single-arm':ti,ab,kw) AND ('trial*':ti,ab,kw OR 'stud*':ti,ab,kw))	
#20	Publication type: real-world or observational studies 'case control study'/exp OR 'cross-sectional study'/exp 'clinical audit'/exp OR 'comparative study':it OR 'observational study':it OR (('comparat*':ti,ab,kw) AND ('trial':ti,ab,kw OR 'stud*':ti,ab,kw)) OR (('case-control':ti,ab,kw OR 'case control':ti,ab,kw OR 'cross-section*':ti,ab,kw OR 'cross section*':ti,ab,kw OR 'cohort':ti,ab,kw OR 'retrospectiv*':ti,ab,kw OR 'longitudinal':ti,ab,kw OR 'prospective':ti,ab,kw OR 'observation*':ti,ab,kw OR 'comparative':ti,ab,kw OR 'non-randomised':ti,ab,kw OR 'non-randomized':ti,ab,kw) AND ('stud*':ti,ab,kw OR 'trial*':ti,ab,kw)) OR 'pragmatic clinical trial':ti,ab,kw OR (('hospital':ti,ab,kw OR 'medical':ti,ab,kw OR 'electronic':ti,ab,kw) AND ('record*':ti,ab,kw OR 'chart*':ti,ab,kw)) OR 'registry':ti,ab,kw OR 'non random':ti,ab,kw OR 'single arm':ti,ab,kw OR 'real world':ti,ab,kw OR 'real life':ti,ab,kw OR 'real world':ti,ab,kw OR 'northstar':ti,ab,kw OR 'north star':ti,ab,kw OR 'registry':ti,ab,kw	5,555,419
#21	#18 OR #19 OR #20	8,812,270
#22	Publication Type: Not required publications (e.g. Comment, Letter, Editorial, Case Reports, Guideline etc.) 'case reports':it OR 'editorial':it OR 'letter':it OR 'comment':it OR 'clinical trial, veterinary':it OR 'guideline':it OR 'news':it OR 'lecture':it OR 'interview':it	2,110,346
#23	Publication Type: Not required publications (e.g. animal studies) 'animal'/exp NOT ('animal'/exp AND 'human'/exp)	6,121,434
#24	#22 OR #23	8,189,807
#25	#21 NOT #24	7,959,763
#26	#1 AND #6 AND #25	272
#27	#1 AND #17 AND #25	1,927
#28	#26 OR #27	2,059

Table 96: Search strategy for Cochrane via the Cochrane Library Advanced Search tool (including CENTRAL) (original search)

No.	Query	Results
#1	“Muscular Dystrophy, Duchenne”[MeSH Term]	947
#2	“Brachial Plexus Neuropathies”[MeSH Term]	96
#3	“Sarcoglycanopathies”[MeSH Term]	2

#4	“Duchenne”[Limits]	983
#5	“Muscular Dystrophy, Duchenne”[Limits]	947
#6	DMD	932
#7	((“Duchenne”) AND (“Dystrophy” OR “Morbus” OR “syndrome”)):ti,ab,kw	936
#8	“becker”[Limits]	4,115
#9	Duchenne becker”[Limits]	90
#10	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7) NOT (#8 OR #9)	1,276
#11	Givinostat	23
#12	Ataluren	127
#13	Delandistrogene moxeparvovec	13
#14	Delandistrogene	13
#15	Fordadistrogene movaparvovec	2
#16	Fordadistrogene	2
#17	established clinical management	9751
#18	clinical management	135,506
#19	steroid*	39,912
#20	corticosteroid*	28,186
#21	glucocorticoid*	11,548
#22	prednisone	11,475
#23	prednisolone	8,715
#24	Deflazacort	236
#25	physiotherap*	28,919
#26	physical therap*	90,524

#27	#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26	293,809
#28	#10 and #27	535

SLR update November 2024

The search strings used to identify relevant studies are provided in Table 97 for MEDLINE®, Table 98 for Embase® and Table 99 for Cochrane.

Table 97: Search strategy for MEDLINE® via PubMed® (updated search)

No.	Query	Results
#1	Disease string ("Muscular Dystrophy, Duchenne"[MeSH] OR (("Duchenne"[Title/Abstract] AND ("dystrophy"[Title/Abstract] OR "morbus"[Title/Abstract] OR "syndrome"[Title/Abstract] OR "muscular"[Title/Abstract])) OR "DMD"[Title/Abstract]) NOT ("becker"[Title/Abstract] OR "Duchenne becker"[Title/Abstract])	15,831
#2	Givinostat "givinostat"[Title/Abstract] OR "ITF2357"[Title/Abstract] OR "ITF 2357"[Title/Abstract] OR "ITF-2357"[Title/Abstract]	160
#3	Ataluren "ataluren"[Title/Abstract] OR "translarna"[Title/Abstract] OR "PTC124"[Title/Abstract] OR "PTC 124"[Title/Abstract] OR "PTC-124"[Title/Abstract]	274
#4	Delandistrogene moxeparvovec "delandistrogene"[Title/Abstract] OR "delandistrogene moxeparvovec"[Title/Abstract] OR "elevidys"[Title/Abstract] OR "SRP-9001"[Title/Abstract] OR "SRP 9001"[Title/Abstract] OR "SRP9001"[Title/Abstract]	19
#5	Fordadistrogene movaparvovec "fordadistrogene"[Title/Abstract] OR "fordadistrogene movaparvovec"[Title/Abstract] OR "PF-06939926"[Title/Abstract] OR "PF 06939926"[Title/Abstract] OR "PF06939926"[Title/Abstract]	1
#6	#2 OR #3 OR #4 OR #5	453
#7	Adrenal cortex hormones "adrenal cortex hormones"[MeSH Terms] OR "Prednisolone"[MeSH Terms] OR "corticosteroid*"[Title/Abstract] OR	696,000

	“glucocorticoid*”[Title/Abstract] OR “prednisone”[Title/Abstract] OR “deflazacort”[Title/Abstract] or “steroid*”[Title/Abstract]	
#8	ACE or ARB inhibitors “angiotensin converting enzyme inhibitors”[MeSH Terms] OR “lisinopril”[MeSH Terms] OR “perindopril”[MeSH Terms] OR “ramipril”[MeSH Terms] OR “ACE inhibitors”[Title/Abstract] OR “lisinopril”[Title/Abstract] OR “perindopril”[Title/Abstract] OR “ramipril”[Title/Abstract] OR “angiotensin receptor antagonists”[MeSH Terms] OR “irbesartan”[MeSH Terms] OR “candesartan”[Supplementary concept] OR “losartan”[MeSH Terms] OR “angiotensin receptor antagonists”[Title/Abstract] OR “irbesartan”[Title/Abstract] OR “candesartan” [Title/Abstract] OR “losartan”[Title/Abstract]	64,522
#9	Beta blockers “beta blockers”[Title/Abstract] OR ”adrenergic beta-antagonists”[MeSH Terms] OR “bisoprolol”[MeSH Terms] “metoprolol”[MeSH Terms] “bisoprolol”[Title/Abstract] “metoprolol”[Title/Abstract] OR “beta blocker*”[Title/Abstract] OR “beta antagonist*”[Title/Abstract] OR “beta-blocker*”[Title/Abstract] OR “beta-antagonist*”[Title/Abstract]	70,647
#10	Heart function preservation “ivabradine”[MeSH Terms] OR “Mineralocorticoids”[MeSH Terms] OR “eplerenone”[MeSH Terms] OR “spironolactone”[MeSH Terms] OR “ivabradine”[Title/Abstract] OR “Mineralocorticoid*”[Title/Abstract] OR “MRA”[Title/Abstract] OR ((“MRA”[Title/Abstract] OR “mineralocorticoid*”[Title/Abstract]) AND (“blocking drug*”[Title/Abstract] OR “blocking-drug*”[Title/Abstract])) OR “eplerenone”[Title/Abstract] OR “spironolactone”[Title/Abstract]	33,910
#11	Neuropsychological therapy 'neuropsycholog*':ti,ab,kw AND ('therap*':ti,ab,kw OR 'treatment':ti,ab,kw)	16,099
#12	Occupational therapy (('occupational':ti,ab,kw) AND ('therap*':ti,ab,kw OR 'treatment':ti,ab,kw)) OR 'occupational therapy'/exp	41,709
#13	Physiotherapy 'physiotherap*':ti,ab,kw OR 'physiotherapy'/exp OR 'physical therap*':ti,ab,kw OR 'HTMF':ti,ab,kw	231,690
#14	Pacemaker 'artificial heart pacemaker'/exp OR ('pacemaker':ti,ab,kw AND 'artificial':ti,ab,kw) OR 'pacemaker':ti,ab,kw OR 'artificial cardiac	55,072

	pacemaker':ti,ab,kw OR ('pacemaker':ti,ab,kw AND ('artificial':ti,ab,kw OR 'cardiac':ti,ab,kw))	
#15	Surgery 'spine surger*':ti,ab,kw OR 'spinal surger*':ti,ab,kw	21,841
#16	Ventilation 'artificial ventilation'/exp OR 'ventilation':ti,ab,kw OR 'artificial respiration':ti,ab,kw	203,280
#17	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16	1,375,235
#18	Publication type: RCTs 'randomized controlled trial (topic)'/exp OR 'clinical trial (topic)'/exp OR 'randomization'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR 'placebo effect'/exp OR 'placebo'/exp OR 'control group'/exp OR 'crossover procedure'/exp OR 'controlled clinical trial':it OR 'clinical trial, phase ii':it OR 'clinical trial, phase iii':it OR 'clinical trial, phase iv':it OR 'rct':ti,ab,kw OR 'randomisation':ti,ab,kw OR 'randomization':ti,ab,kw OR 'randomised controlled trial':ti,ab,kw OR 'randomized controlled trial':ti,ab,kw OR (('random*':ti,ab,kw) AND ('trial':ti,ab,kw OR 'control*':ti,ab,kw OR 'assign*':ti,ab,kw OR 'allocat*':ti,ab,kw OR 'stud*':ti,ab,kw OR 'clinical':ti,ab,kw)) OR (('placeb*':ti,ab,kw) AND ('trial':ti,ab,kw OR 'control*':ti,ab,kw OR 'assign*':ti,ab,kw OR 'allocat*':ti,ab,kw OR 'stud*':ti,ab,kw OR 'clinical':ti,ab,kw)) OR (('control*':ti,ab,kw) AND ('clinical':ti,ab,kw OR 'trial':ti,ab,kw OR 'group':ti,ab,kw)) OR 'control group':ti,ab,kw OR (('single':ti,ab,kw OR 'double':ti,ab,kw OR 'triple':ti,ab,kw OR 'treble':ti,ab,kw) AND ('blind':ti,ab,kw OR 'blind*':ti,ab,kw OR 'mask':ti,ab,kw OR 'mask*':ti,ab,kw)) OR 'open label':ti,ab,kw OR 'open-label':ti,ab,kw OR 'clinical study':ti,ab,kw OR 'clinical article':ti,ab,kw	3,342,394
#19	Publication type: single-arm trials 'single arm':ti,ab,kw OR 'single-arm':ti,ab,kw OR (('single arm':ti,ab,kw OR 'single-arm':ti,ab,kw) AND ('trial*':ti,ab,kw OR 'stud*':ti,ab,kw))	16,120
#20	Publication type: real-world or observational studies 'case control study'/exp OR 'cross-sectional study'/exp 'clinical audit'/exp OR 'comparative study':it OR 'observational study':it OR (('comparat*':ti,ab,kw) AND ('trial':ti,ab,kw OR 'stud*':ti,ab,kw)) OR (('case-control':ti,ab,kw OR 'case control':ti,ab,kw OR 'cross-section*':ti,ab,kw OR 'cross section*':ti,ab,kw OR 'cohort':ti,ab,kw OR 'retrospectiv*':ti,ab,kw OR 'longitudinal':ti,ab,kw OR 'prospective':ti,ab,kw OR 'observation*':ti,ab,kw OR 'comparative':ti,ab,kw OR 'non-randomised':ti,ab,kw OR 'non-randomized':ti,ab,kw) AND ('stud*':ti,ab,kw OR 'trial*':ti,ab,kw)) OR 'pragmatic clinical trial':ti,ab,kw OR (('hospital':ti,ab,kw OR 'medical':ti,ab,kw OR 'electronic':ti,ab,kw) AND ('record*':ti,ab,kw OR 'chart*':ti,ab,kw)) OR 'registry':ti,ab,kw OR 'non random':ti,ab,kw OR 'single arm':ti,ab,kw OR 'real world':ti,ab,kw OR 'real	6,863,469

	life':ti,ab,kw OR 'real world':ti,ab,kw OR 'northstar':ti,ab,kw OR 'north star':ti,ab,kw OR 'registry':ti,ab,kw	
#21	#18 OR #19 OR #20	8,788,905
#22	Publication Type: Not required publications (e.g. Comment, Letter, Editorial, Case Reports, Guideline etc.) 'case reports':it OR 'editorial':it OR 'letter':it OR 'comment':it OR 'clinical trial, veterinary':it OR 'guideline':it OR 'news':it OR 'lecture':it OR 'interview':it	4,790,240
#23	Publication Type: Not required publications (e.g. animal studies) 'animal'/exp NOT ('animal'/exp AND 'human'/exp)	5,272,703
#24	#22 OR #23	9,930,215
#25	#21 NOT #24	7,511,513
#26	#1 AND #6 AND #25	56
#27	#1 AND #17 AND #25	783
#28	#26 OR #27	815
#29	#28 AND 2024/5/8:3000/12/12[pdat]	32

Table 98: Search strategy for Embase® via Embase® (updated search)

No.	Query	Results
#1	Disease string ('Duchenne muscular dystrophy'/syn OR ('duchenne':ti,ab,kw AND ('dystrophy':ti,ab,kw OR 'morbus':ti,ab,kw OR 'syndrome':ti,ab,kw OR 'muscular':ti,ab,kw)) OR 'dmd':ti,ab,kw) NOT ('becker':ti,ab,kw OR 'duchenne becker':ti,ab,kw)	26,242
#2	Givinostat 'givinostat':ti,ab,kw OR 'itf2357':ti,ab,kw OR 'itf 2357':ti,ab,kw OR 'itf-2357':ti,ab,kw	288
#3	Ataluren 'ataluren':ti,ab,kw OR 'translarna':ti,ab,kw OR 'ptc124':ti,ab,kw OR 'ptc 124':ti,ab,kw OR 'ptc-124':ti,ab,kw	677
#4	Delandistrogene moxeparvovec	82

	'delandistrogene':ti,ab,kw OR 'delandistrogene moxeparvovec':ti,ab,kw OR 'elevidys':ti,ab,kw OR 'srp-9001':ti,ab,kw OR 'srp 9001':ti,ab,kw OR 'srp9001':ti,ab,kw	
#5	Fordadistrogene movaparvovec 'fordadistrogene':ti,ab,kw OR 'fordadistrogene movaparvovec':ti,ab,kw OR 'pf-06939926':ti,ab,kw OR 'pf 06939926':ti,ab,kw OR 'pf06939926':ti,ab,kw	6
#6	#2 OR #3 OR #4 OR #5	1,053
#7	Adrenal cortex hormones 'corticosteroid'/exp OR 'prednisolone'/exp OR 'corticosteroid*':ti,ab,kw OR 'glucocorticoid*':ti,ab,kw OR 'prednisone':ti,ab,kw OR 'deflazacort':ti,ab,kw OR 'prednisolone':ti,ab,kw OR 'steroid*':ti,ab,kw	1,591,689
#8	ACE inhibitors 'dipeptidyl carboxypeptidase inhibitor'/exp OR 'lisinopril'/exp OR 'perindopril'/exp OR 'ramipril'/exp OR 'ace inhibitor*':ti,ab,kw OR 'lisinopril':ti,ab,kw OR 'perindopril':ti,ab,kw OR 'ramipril':ti,ab,kw OR 'angiotensin receptor antagonist'/exp OR 'irbesartan'/exp OR 'losartan'/exp OR 'angiotensin receptor antagonist*':ti,ab,kw OR 'irbesartan':ti,ab,kw OR 'candesartan':ti,ab,kw OR 'losartan':ti,ab,kw	274,343
#9	Beta blockers 'beta blockers':ti,ab,kw OR 'beta adrenergic receptor blocking agent'/exp OR 'bisoprolol'/exp OR 'metoprolol'/exp OR 'bisoprolol':ti,ab,kw OR 'metoprolol':ti,ab,kw OR 'beta blocker*':ti,ab,kw OR 'beta antagonist*':ti,ab,kw OR 'beta-blocker*':ti,ab,kw OR 'beta-antagonist*':ti,ab,kw	367,638
#10	Heart function preservation 'ivabradine'/exp OR 'mineralocorticoid'/exp OR 'eplerenone'/exp OR 'spironolactone'/exp OR 'ivabradine':ti,ab,kw OR 'mineralocorticoid*':ti,ab,kw OR 'mra':ti,ab,kw OR (('mra':ti,ab,kw OR 'mineralocorticoid*':ti,ab,kw) AND ('blocking drug*':ti,ab,kw OR 'blocking-drug*':ti,ab,kw)) OR 'eplerenone':ti,ab,kw OR 'spironolactone':ti,ab,kw	167,051
#11	Neuropsychological therapy 'neuropsycholog*':ti,ab,kw AND ('therap*':ti,ab,kw OR 'treatment':ti,ab,kw)	26,835
#12	Occupational therapy (('occupational':ti,ab,kw) AND ('therap*':ti,ab,kw OR 'treatment':ti,ab,kw)) OR 'occupational therapy'/exp	66,414

#13	Physiotherapy 'physiotherap*':ti,ab,kw OR 'physiotherapy'/exp OR 'physical therap*':ti,ab,kw OR 'HTMF':ti,ab,kw	172,665
#14	Pacemaker 'artificial heart pacemaker'/exp OR ('pacemaker':ti,ab,kw AND 'artificial':ti,ab,kw) OR 'pacemaker':ti,ab,kw OR 'artificial cardiac pacemaker':ti,ab,kw OR ('pacemaker':ti,ab,kw AND ('artificial':ti,ab,kw OR 'cardiac':ti,ab,kw))	87,155
#15	Surgery 'spine surger*':ti,ab,kw OR 'spinal surger*':ti,ab,kw	28,984
#16	Ventilation 'artificial ventilation'/exp OR 'ventilation':ti,ab,kw OR 'artificial respiration':ti,ab,kw	413,214
#17	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16	2,795,512
#18	Publication type: RCTs 'randomized controlled trial (topic)'/exp OR 'clinical trial (topic)'/exp OR 'randomization'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR 'placebo effect'/exp OR 'placebo'/exp OR 'control group'/exp OR 'crossover procedure'/exp OR 'controlled clinical trial':it OR 'clinical trial, phase ii':it OR 'clinical trial, phase iii':it OR 'clinical trial, phase iv':it OR 'rct':ti,ab,kw OR 'randomisation':ti,ab,kw OR 'randomization':ti,ab,kw OR 'randomised controlled trial':ti,ab,kw OR 'randomized controlled trial':ti,ab,kw OR (('random*':ti,ab,kw) AND ('trial':ti,ab,kw OR 'control*':ti,ab,kw OR 'assign*':ti,ab,kw OR 'allocat*':ti,ab,kw OR 'stud*':ti,ab,kw OR 'clinical':ti,ab,kw)) OR (('placeb*':ti,ab,kw) AND ('trial':ti,ab,kw OR 'control*':ti,ab,kw OR 'assign*':ti,ab,kw OR 'allocat*':ti,ab,kw OR 'stud*':ti,ab,kw OR 'clinical':ti,ab,kw)) OR (('control*':ti,ab,kw) AND ('clinical':ti,ab,kw OR 'trial':ti,ab,kw OR 'group':ti,ab,kw)) OR 'control group':ti,ab,kw OR (('single':ti,ab,kw OR 'double':ti,ab,kw OR 'triple':ti,ab,kw OR 'treble':ti,ab,kw) AND ('blind':ti,ab,kw OR 'blind*':ti,ab,kw OR 'mask':ti,ab,kw OR 'mask*':ti,ab,kw)) OR 'open label':ti,ab,kw OR 'open-label':ti,ab,kw OR 'clinical study':ti,ab,kw OR 'clinical article':ti,ab,kw	4,637,972
#19	Publication type: single arm trials 'single arm':ti,ab,kw OR 'single-arm':ti,ab,kw OR (('single arm':ti,ab,kw OR 'single-arm':ti,ab,kw) AND ('trial*':ti,ab,kw OR 'stud*':ti,ab,kw))	33,409
#20	Publication type: real-world or observational studies 'case control study'/exp OR 'cross-sectional study'/exp OR 'clinical audit'/exp OR 'comparative study':it OR 'observational study':it OR	6,018,870

	(('comparat*':ti,ab,kw) AND ('trial':ti,ab,kw OR 'stud*':ti,ab,kw)) OR (('case-control':ti,ab,kw OR 'case control':ti,ab,kw OR 'cross-section*':ti,ab,kw OR 'cross section*':ti,ab,kw OR 'cohort':ti,ab,kw OR 'retrospectiv*':ti,ab,kw OR 'longitudinal':ti,ab,kw OR 'prospective':ti,ab,kw OR 'observation*':ti,ab,kw OR 'comparative':ti,ab,kw OR 'non-randomised':ti,ab,kw OR 'non-randomized':ti,ab,kw) AND ('stud*':ti,ab,kw OR 'trial*':ti,ab,kw)) OR 'pragmatic clinical trial':ti,ab,kw OR (('hospital':ti,ab,kw OR 'medical':ti,ab,kw OR 'electronic':ti,ab,kw) AND ('record*':ti,ab,kw OR 'chart*':ti,ab,kw)) OR 'registry':ti,ab,kw OR 'non random':ti,ab,kw OR 'single arm':ti,ab,kw OR 'real world':ti,ab,kw OR 'real life':ti,ab,kw OR 'real world':ti,ab,kw OR 'northstar':ti,ab,kw OR 'north star':ti,ab,kw OR 'registry':ti,ab,kw	
#21	#18 OR #19 OR #20	9,310,043
#22	Publication Type: Not required publications (e.g. Comment, Letter, Editorial, Case Reports, Guideline etc.) 'case reports':it OR 'editorial':it OR 'letter':it OR 'comment':it OR 'clinical trial, veterinary':it OR 'guideline':it OR 'news':it OR 'lecture':it OR 'interview':it	2,153,091
#23	Publication Type: Not required publications (e.g. animal studies) 'animal'/exp NOT ('animal'/exp AND 'human'/exp)	6,202,877
#24	#22 OR #23	8,313, 477
#25	#21 NOT #24	8,424,203
#26	#1 AND #6 AND #25	301
#27	#1 AND #17 AND #25	2,076
#28	#26 OR #27	2,222
#29	#28 AND [08-05-2024]/sd NOT [02-12-2024]/sd	134

Table 99: Search strategy for Cochrane via the Cochrane Library Advanced Search tool (includes CENTRAL (updated search)

No.	Query	Results
#1	MeSH descriptor: [Muscular Dystrophy, Duchenne] explode all trees	356

#2	MeSH desciptor: [Brachial Plexus Neuropathies] explode all trees	98
#3	MeSH descriptor: [Sarcoglycanopathies] explode all trees	2
#4	Duchenne	1,021
#5	Muscular Dystrophy, Duchenne	981
#6	DMD	961
#7	((Duchenne) AND (Dystrophy OR Morbus OR syndrome)):ti,ab,kw	965
#8	becker	4,205
#9	Duchenne becker	89
#10	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7) NOT (#8 OR #9)	1,318
#11	Givinostat	29
#12	Ataluren	129
#13	Delandistrogene moxeparvovec	17
#14	Delandistrogene	17
#15	Fordadistrogene movaparvovec	3
#16	Fordadistrogene	3
#17	established clinical management	9,942
#18	clinical management	141,298
#19	steroid*	40,711
#20	corticosteroid*	29,072
#21	glucocorticoid*	11,832
#22	prednisone	11,744
#23	prednisolone	8,883
#24	Deflazacort	243
#25	physiotherap*	30,524

#26	physical therap*	94,716
#27	#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26	305,793
#28	#10 and #27	553
#29	Manual limitation of #28 from April 2024 to present (8th November 2024)	28

Systematic selection of studies

The search results were exported to EndNote and de-duplicated. Each publication was then screened against pre-defined eligibility (inclusion and exclusion) PICOS criteria (0), in Microsoft Excel® to establish which studies were eligible for inclusion. Initially, citations were screened by title and abstract (first-pass stage). Each citation was screened by two independent reviewers and any discrepancies between the reviewers were reconciled through consensus or a third independent reviewer. Citations that did not match the eligibility criteria, and duplicate citations owing to overlap in the coverage of databases, were excluded at the first-pass stage; wherever unclear, citations were included. Full-text articles were retrieved for potentially relevant studies that were eligible after first-pass screening. Each full text was screened by two independent reviewers, using the same pre-defined eligibility PICOS criteria, and any discrepancies between reviewers were reconciled by a third independent reviewer.

Eligibility criteria

The prespecified eligibility criteria for the original SLR are detailed in Table 100.

Table 100: Clinical SLR | Eligibility (PICOS) criteria for the original global SLR

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Population	• Patients with a diagnosis of DMD or parents/caregivers who provide responses on their behalf (e.g. proxies) • Clinicians who manage patients with DMD	Other muscular dystrophies including Becker muscular dystrophy	NA
Intervention	• Givinostat • Ataluren • Delandistrogene moxeparvovec	• Analgesia (except w.r.t. Corticosteroids) • Complementary medicines	NA

	• Fordadistrogene movaparvovec • ECM (to include most or all of adrenal cortex hormones/corticosteroids, ACE inhibitors, beta blockers, neuropsychological therapy, occupational therapy, physiotherapy, spinal surgery, and ventilation)	• Psychological therapy (e.g. CBT)	
Comparators	ANY	NA	NA
Outcomes	• Natural history data for disease course • Efficacy (including but not limited to) o 4SC o Walking ability (ambulation), e.g. using the 6MWT or 10-meter walking test o TTR o Ambulation, e.g. using time to wheelchair, NSAA, or number of falls o Ventilation outcomes, including non-invasive night-time ventilation and full ventilation o Vastus lateralis fat fraction o Muscle strength, e.g. using hand-to-mouth function, knee flexion or extension, elbow flexion or extension o Cardiac function, e.g. using ECG or ECHO o Lung function, e.g. FVC o Time to scoliosis • Safety o Mortality	Outcomes not listed	NA

	o Adverse effects of treatment • PROs o Utility data (utility data will be cross checked in the identified studies in addition to the utility searches • Correlation between outcomes in ambulatory and non-ambulatory patients, meeting all three of the following criteria: o Compare at least two interventions (one can be placebo) o Have an "early" endpoint e.g. some in the ambulatory phase (could be walking endpoint, standing, climbing, and loss of ambulation) o Have a "late" endpoint in the non-ambulatory phase e.g. loss of hand-to-mouth function, respiratory, cardiac, mortality		
Study design/publication type	• Randomised-controlled trials • Single-arm trials • Real-world/observational studies (including retrospective or prospective cohort analyses, longitudinal studies, naturalistic studies, database analyses, registries, surveys) reporting clinical outcomes • SLRs of clinical evaluations (for reference checking only)	• Non-systematic reviews • Editorials, comments, letters, case reports, case series • Phase 1 • Animal studies	NA
Language restrictions	English language	English language abstracts of foreign language publications	NA

		will be considered for inclusion	
Date of publication	• Full publication: No time limit • Conference abstract: May 2022 to present	NA	NA
Countries	No restriction	NA	NA

Abbreviations: 4SC, 4-stair climb; 6MWT, 6-minute walk test; ACE, angiotensin-converting enzyme; CBT, cognitive behavioural therapy; DMD, Duchenne muscular dystrophy; ECG, electrocardiogram; ECHO, echocardiogram; ECM, established clinical management; FVC, forced vital capacity; N/A, not applicable; NSAA, North Star Ambulatory Assessment; PRO, patient-reported outcome; SLR, systematic literature review; TTR, time to rise from floor.

To align with the decision problem, a final dual-screening step was conducted using the adapted eligibility criteria shown in Table 101. This ensured that the final list of included studies only included evidence relevant to the decision problem.

Table 101: Clinical SLR | Eligibility (PICOS) criteria relevant to the decision problem for the original SLR

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Population	Patients with a diagnosis of DMD or parents/caregivers who provide responses on their behalf (e.g. proxies) 6 years and over	Other muscular dystrophies including Becker muscular dystrophy	NA
Intervention	• Givinostat • ECM without givinostat from multinational or UK natural history studies	Intervention not listed	NA
Comparators	Any		NA
Outcomes	The outcome measures to be considered include, but not limited to: • Efficacy o 4SC o Walking ability (ambulation), e.g. using the 6MWT or 10-meter walking test o TTR		Outcomes not listed

	o Ambulation, e.g. using time to wheelchair, NSAA, or number of falls o Ventilation outcomes, including non-invasive night-time ventilation and full ventilation o Vastus lateralis fat fraction o Muscle strength, e.g. using hand-to-mouth function, knee flexion or extension, elbow flexion or extension o Cardiac function, e.g. using ECG or ECHO o Lung function, e.g. FVC o Time to scoliosis • Safety o Mortality o Adverse effects of treatment Utility data will be cross checked in the identified studies in addition to the utility searches	
Study design/publication type	• Randomised-controlled trials • Single-arm trials • Real-world/observational studies (including retrospective or prospective cohort analyses, longitudinal studies, naturalistic studies, database	• Non-systematic reviews • Editorials, comments, letters, case reports, case series • Phase 1

	analyses, registries, surveys) reporting clinical outcomes • SLRs of clinical evaluations (for reference checking only)	• Animal studies
Language restrictions	English language	English language abstracts of foreign language publications will be considered for inclusion
Date of publication	Full publication: No time limit Conference abstract: May 2022 to present	NA
Countries	• No restriction for givinostat studies • Multinational or UK registry studies for ECM	NA

Abbreviations: 4SC, 4-stair climb; 6MWT, 6-minute walk test; DMD, Duchenne muscular dystrophy; ECG, electrocardiogram; ECHO, echocardiogram; ECM, established clinical management; FVC, forced vital capacity; N/A, not applicable; NSAA, north star ambulatory assessment; SLR, systematic literature review; TTR, time to rise from floor; UK, United Kingdom.

For the SLR update carried out in November 2024, the focus was to identify any new givinostat data or UK-specific natural history data published since the prior SLR. The eligibility criteria used are shown in Table 102.

Table 102: | Clinical SLR | Eligibility (PICOS) criteria relevant to the decision problem for the SLR update

	Inclusion criteria	Exclusion criteria
Population	Patients with a diagnosis of DMD or parents/caregivers who provide responses on their behalf (e.g. proxies) 6 years and over	Other muscular dystrophies including Becker muscular dystrophy
Intervention	Givinostat ECM without givinostat or UK natural history studies	Intervention not listed
Comparators	Any	Comparator not listed

Outcomes	The outcome measures to be considered include, but are not limited to: • Efficacy • 4SC • Walking ability (ambulation), e.g. using the 6MWT or 10-meter walking test • TTR • Ambulation e.g. using time to wheelchair, NSAA, or number of falls • Ventilation outcomes, including non-invasive nighttime ventilation and full ventilation • Vastus lateralis fat fraction • Muscle strength, e.g. using hand-to-mouth function, knee flexion or extension, elbow flexion or extension • Cardiac function, e.g. using ECG or ECHO • Lung function, e.g. FVC • Time to scoliosis • Safety • Mortality • Adverse effects of treatment Utility data will be cross-checked in the identified studies in addition to the utility searches	Outcomes not listed
Study design	RCTs Single-arm trials Real-world/observational studies (including retrospective or prospective cohort analyses, longitudinal studies, naturalistic studies, database analyses, registries, surveys) reporting clinical outcomes SLRs of clinical evaluations (for reference checking only)	Non-systematic reviews Editorials, comments, letters, case reports, case series Phase 1 Animal studies
Language	English language	English language abstracts of foreign language publications will be considered for inclusion
Date of publication	Full publication: from original SLR search date to present Conference abstract: from original SLR search date to present	N/A

Countries	No restriction for givinostat studies UK registry studies for ECM	N/A

Abbreviations: 4SC, 4-stair climb; 6MWT, 6-minute walk test; DMD, Duchenne muscular dystrophy; ECG, electrocardiogram; ECHO, echocardiogram; ECM, established clinical management; FVC, forced vital capacity; N/A, not applicable; NSAA, north star ambulatory assessment; RCT, randomised controlled trial; SLR, systematic literature review; TTR, time to rise from floor; UK, United Kingdom.

Results

For the original SLR, of the 3,381 papers identified by the database searches, 651 were removed as duplicates, and the titles and abstracts of 2,730 papers were reviewed at first-pass screening. After exclusion of 2,617 papers, the full texts of 113 publications were reviewed at second-pass screening, of which 59 were subsequently excluded. A total of 54 met the pre-defined inclusion criteria from the database searches and were included in the review.

Of the 273 papers identified by the grey literature searches, 211 were excluded at first-pass screening. Additionally, two publications were identified through hand searching. Of the 64 publications that were reviewed as full-text articles, 23 were excluded and 41 met the selection criteria for inclusion in the clinical SLR.

Therefore, a total of 95 publications were reviewed for relevance to the final appraisal decision problem, as per the pre-defined eligibility criteria described in Appendix H. In total, 48 publications were excluded and 47 publications were included. The flow of studies through the reviews is reported in the preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram in

Figure 56.

An update of the SLR was run, for the period 07 May 2024 to 07-08 November 2024. Five new publications were identified. The flow of studies through the reviews is reported in the PRISMA flow diagram in Figure 57.

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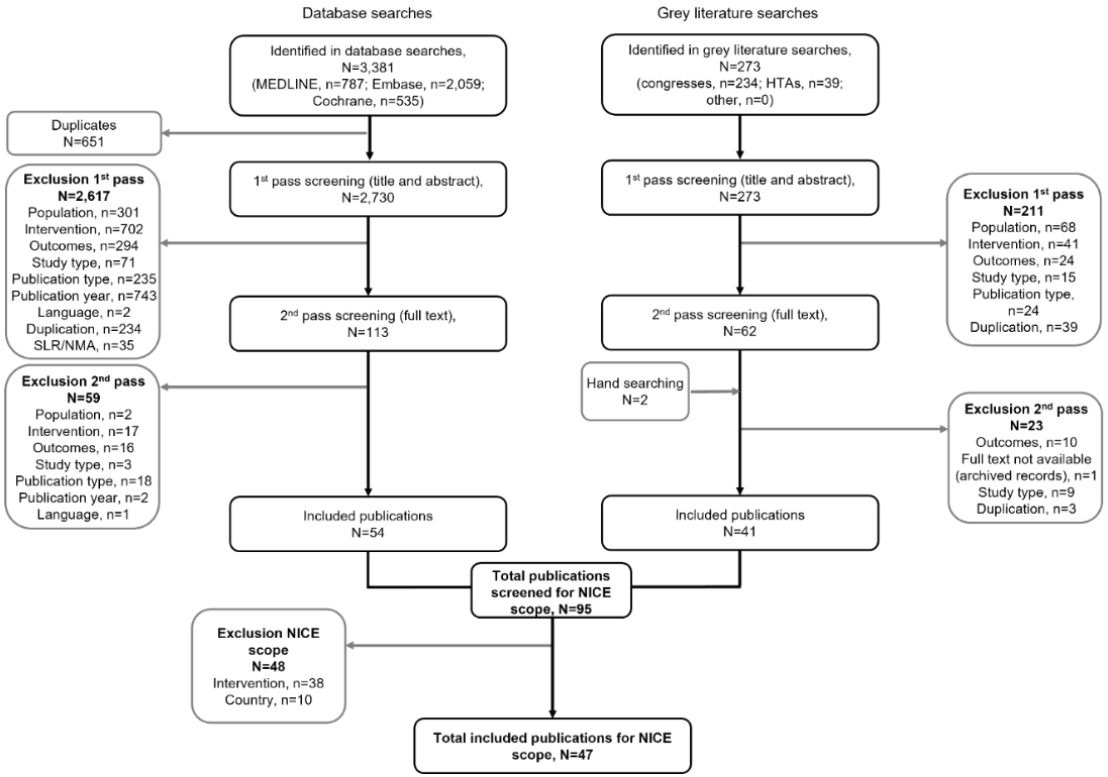
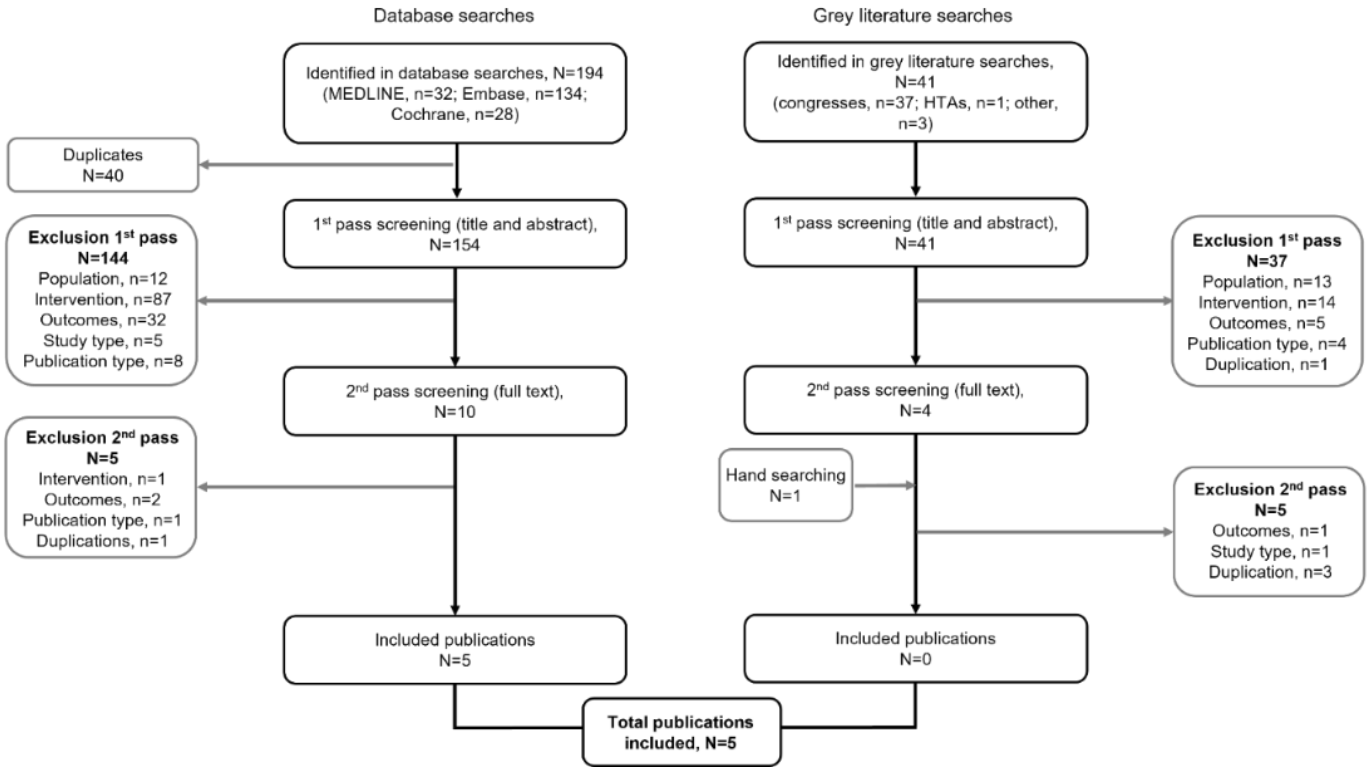
Figure 56: PRISMA flow diagram of the original clinical SLR



Abbreviations: HTA, health technology assessment; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; PRISMA, preferred reporting items for systematic reviews and meta-analyses; SLR, systematic literature review

Figure 57: PRISMA flow diagram of the clinical SLR update



Abbreviations: HTA, health technology assessment; PRISMA, preferred reporting items for systematic reviews and meta-analyses; SLR, systematic literature review

An overview of the study design of studies included in this application is provided in Table 103.

Table 103: Overview of study design for studies included in the analyses

Study/ID	Aim	Study design	Patient population	Interven-tion and compara-tor (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
EPIDYS/ NCT02851797	To evaluate givinostat efficacy and safety in ambulant DMD patients 6 years and older over a period of 72 weeks	Multicentre, randomised, double-blind, placebo-controlled, phase 3 trial	179 male ambulant subjects were randomized 2:1 (givinostat: placebo) stratified by concomitant steroid use. Eligible participants were ambulant male patients aged at least 6 years with genetically confirmed Duchenne muscular dystrophy	Intervention: Givinostat + GCs Comparator: Placebo + GCs	Standard 4SC assessment (baseline and 18 months)	**Secondary endpoints** NSAA total score (baseline and 18 months) NSAA cumulative loss of function (baseline and 18 months) Time-to-rise from floor (baseline and 18 months) Distance walked in 6 minutes (baseline and 18 months) Muscle strength evaluated by knee extension (baseline and 18 months) Muscle strength

Study/ID	Aim	Study design	Patient population	Interven-tion and compara-tor (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
						evaluated by elbow flexion measured by HHM (baseline and 18 months) Mean change in VL MFF (baseline and 18 months)
OLE (Study 51)/ NCT03373968	To assess the safety, tolerability, and efficacy of givinostat in male DMD patients previously enrolled in one of the other DMD givinostat studies, who have completed the previous study and tolerated the study drug, and givinostat-naïve DMD patients	Open-label, single arm long-term follow-up phase 2/3 study (ongoing, enrolling by invitation)	Patients who have participated in one of the previous studies with givinostat in DMD. n = 207 enrolled at the fifth interim analysis cut-off date (31 Dec 2023)	Intervention: Givinostat + GCs Comparator: NA	Type, incidence, and severity of treatment-related/not related AEs and serious TEAEs (baseline, week 48 and yearly until end of study)	**Secondary endpoints (ambulant patients)** Physical functions, including 6MWD, NSAA, and Time function tests, such as TRF, 4SC, 4SC velocity, and 10MWT (Week 48 and then yearly until the end of study) Muscle strength assessment, focusing on knee extension

Study/ID	Aim	Study design	Patient population	Interven-tion and compara-tor (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
						and elbow flexion, measured by HHM (Week 48 and then yearly until the end of study) **Secondary endpoints (non-ambulant patients)** Physical function assessment using the EK score Evaluation of activities of daily living through patient and caregiver reports, measured by the Barthel Index
UK real-world data study, NA	To present real-world data on outcomes for adult patients with DMD	A multicentre retrospecti ve case note review	Adults with DMD	GCs (n: 219)	Loss of ambulation NIV FVC Participant s had	NA

Study/ID	Aim	Study design	Patient population	Interven-tion and compara-tor (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
	treated with GCs				assessments at baseline and Months 3, 6, 9, and 12 (ambulatory), or Months 6 and 12 (non-ambulatory). Long-term follow-up visits were at Months 18, 24, and annually thereafter.	

Excluded fulltext references

Overall, 2,958 publications were excluded in the original clinical SLR. 2,617 were excluded during first-pass screening and 59 were excluded during second-pass screening through database searches. Through grey literature searches, 211 were excluded during first-pass screening and 23 were excluded during second-pass screening. During the final screening step relevant to the decision problem, a final 48 publications were excluded.

For the SLR update, a total of 191, publications were excluded; for the database searches 144 were excluded during first-pass screening and five during second-pass screening and for the grey literature searches 37 were excluded during first-pass screening and five during second-pass screening.

Due to the large number of studies excluded, these are attached as separate files: Italfarmaco (2024i), Italfarmaco (2024j), Italfarmaco (2024k), Italfarmaco (2024l), Italfarmaco (2024m), Italfarmaco (2024n).

A full list of the studies included during second-pass screening is presented in Table 104

Table 104: List of studies included in the clinical SLR based on the PICOS criteria relevant to the decision problem

Authors	Year	Title	Relevance for ITC	Notes
Givinostat studies				
E. Mercuri; J. J. Vilchez; O. Boespflug-Tanguy; et al.	2024	Safety and efficacy of givinostat in boys with Duchenne muscular dystrophy (EPIDYS): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial	Not applicable – givinostat publication	We included all givinostat clinical trial studies for which patient-level data were available to inform the givinostat arm in the ITC (EPIDYS; Study 43; Study 51) and these studies are not relevant for identifying ECM comparator data with a long follow up period (>18 mths)
Eugenio Maria Mercuri, Claudia Brogna, Craig Zaidman, Katherine Mathews, et al.	2024	M163: The EPIDYS Givinostat Study in DMD: supportive results	Not applicable – givinostat publication	As above
Simonetta Andrea Licandro, Stefania Petrini, Krista Vandenborne, et al.	2024	S71: Givinostat effects on DMD pathogenesis	Not applicable – givinostat publication	As above
C. Mcdonald, L. Servais, F. Munell, et al.	2024	P369: Givinostat in Duchenne muscular dystrophy: effect on disease milestones	Not applicable – givinostat publication	As above

K. Vanderborne, R. Willcocks, G. Walter, et al.	2024	P370: Givinostat in DMD: results of the EPIDYS Study with particular attention to MR measures of muscle fat fraction	Not applicable – givinostat publication	As above
E. Mercuri, C. Brogna, J. Mah, et al.	2024	P371: Givinostat in DMD: results of the EPIDYS Study with particular attention to NSAA	Not applicable – givinostat publication	As above
K. Vandenborne; R. Willcocks; G. Walter; et al.	2023	Givinostat in DMD: results of the EPIDYS study with particular attention to MR measures of muscle fat fraction	Not applicable – givinostat publication	As above
E. Mercuri; C. Brogna; J. Mah; et al.	2023	Givinostat in DMD: results of the EPIDYS Study with particular attention to NSAA	Not applicable – givinostat publication	As above
C. McDonald; L. Servais; F. Munell; et al.	2023	Givinostat in Duchenne muscular dystrophy: effect on disease milestones	Not applicable – givinostat publication	As above
Eugenio Mercuri, Claudia Brogna, Jean K. Mah, et al.	2023	P99: Givinostat in DMD: results of the EPIDYS Study with particular attention to NSAA	Not applicable – givinostat publication	As above

Krista Vandenborne, Rebecca Willcocks, Glenn Walter, et al.	2023	P113: Givinostat in DMD: results of the EPIDYS Study with particular attention to MR measures of muscle fat fraction	Not applicable – givinostat publication	As above
E. Mercuri; J. Vilchez; O. Boespflug-Tanguy; et al.	2022	O.13 Givinostat in DMD: results of the EPIDYS Study	Not applicable – givinostat publication	As above
Paolo Umberto Bettica	2022	Update on the development of Givinostat in DMD	Not applicable – givinostat publication	As above
D. Vučinić; A. Nascimento; R. Finkel; et al.	2024	Short-term and long-term safety profile of Givinostat in Duchenne muscular dystrophy	Not applicable – givinostat publication	As above
D.G. Andres; V. Sansone; H. Phan; et al.	2024	Givinostat in Duchenne muscular dystrophy: natural history comparison applying propensity score matching	Not applicable – givinostat publication	As above
Pietrusz A, Astin R, Guglieri M, et al.	2024	P39 The effect of corticosteroid treatment on pulmonary function	Yes	Included in base case, multiple outcomes of interest reported for a UK cohort

		in adults with Duchenne muscular dystrophy		
Pietrusz A	NR	Natural history of DMD cohort attending Neuromuscular Service National Hospital for Neurology and Neurosurgery, Queen Square, London	Yes	Included, publication linked with study in row above
Christian Werner, Shiwen Wu, Sheffali Gulati, et al.	2024	M166: Ataluren delays clinically meaningful milestones of decline in 6MWD in patients with nmDMD from Study 041, a phase 3, placebo-controlled trial	Ataluren study	Trial includes placebo arm but only short-term follow-up (72 weeks only)
Christian Werner, Eugenio Maria Mercuri, Francesco Muntoni, et al.	2024	T328: Age at loss of ambulation in patients with DMD from the STRIDE Registry and the CINRG Natural History Study: a matched cohort analysis	STRIDE vs CINRG	Conf abstract with insufficient detail
Christian Werner, Már Tulinius, Filippo Buccella, et al.	2024	T327: Pulmonary function in patients with Duchenne muscular dystrophy from the STRIDE Registry and CINRG Natural History Study: a matched cohort analysis	STRIDE vs CINRG	Conf abstract with insufficient detail

G. Stimpson; D. Ridout; A. Wolfe; E. Milev; E. O'Reilly; A. Manzur; A. Sarkozy; F. Muntoni; T. J. Cole; G. Baranello	2024	Quantifying Variability in Motor Function in Duchenne Muscular Dystrophy: UK Centiles for the NorthStar Ambulatory Assessment, 10 m Walk Run Velocity and Rise from Floor Velocity in GC Treated Boys	Participants from the UK NorthStar registry	Outcomes not of interest for economic model and no baseline characteristics reported; includes assessment only up to 16 years (when boys start to transition to adult services)
E. Mercuri; F. Muntoni; F. Buccella; et al.	2023	Age at loss of ambulation in patients with DMD from the STRIDE registry and the CINRG natural history study: a matched cohort analysis	STRIDE vs CINRG	Conf abstract with insufficient detail
E. Mercuri; A. N. Osorio; F. Muntoni; et al.	2023	Correction to: Safety and effectiveness of ataluren in patients with nonsense mutation DMD in the STRIDE Registry compared with the CINRG Duchenne Natural History Study (2015-2022): 2022 interim analysis	Yes. STRIDE vs CINRG	Erratum to main paper that is included in the ITC SA (see below)
J. Broomfield; K. Abrams; N. Latimer; et al.	2023	Natural history of Duchenne muscular dystrophy in the United Kingdom: A descriptive study	CPRD (Clinical Practice Research Database): GOLD and Aurum	No baseline characteristic data available; no outcomes of interest

		using the Clinical Practice Research Datalink		
V. Laugel; S. D. Lucia; J. Davion; et al.	2023	Preliminary Results from a Prospective, Multicentric, Follow Up Standardized Cohort to Assess Natural History of Duchenne muscular dystrophy	The analysis includes 48 patients with at least 6 months follow up (mean=13.5 months) from France and UK	Conf abstract with insufficient detail
M. Tulinius; F. Buccella; I. Desguerre; et al.	2023	Pulmonary function in patients with Duchenne muscular dystrophy from the STRIDE registry and CINRG natural history study: a matched cohort analysis	STRIDE vs CINRG	Conf abstract with insufficient detail
E. Mercuri; A. N. Osorio; F. Muntoni; et al.	2023	Safety and effectiveness of ataluren in patients with nonsense mutation DMD in the STRIDE Registry compared with the CINRG Duchenne Natural History Study (2015-2022): 2022 interim analysis	Yes. STRIDE vs CINRG	Included in ITC SA, multiple outcomes of interest reported for the subgroup of CINRG patients
Pannie (Panayiota) Trifillis, Eugenio Mercuri, Francesco Muntoni, et al.	2023	P186: Age at loss of ambulation in patients with DMD from the STRIDE Registry and the CINRG	STRIDE vs CINRG	Conf abstract with insufficient detail

		Natural History Study: a matched cohort analysis		
Christian Werner, Már Tulinius, Filippo Buccella, et al.	2023	P116: Pulmonary function in patients with Duchenne muscular dystrophy from the STRIDE Registry and CINRG Natural History Study: a matched cohort analysis	STRIDE vs CINRG	Conf abstract with insufficient detail
Christian Werner, Már Tulinius, Filippo Buccella, et al.	2023	EPNS23-2070: Pulmonary function in patients with Duchenne muscular dystrophy from the STRIDE Registry and CINRG Natural History Study: a matched cohort analysis	STRIDE vs CINRG	Conf abstract with insufficient detail
Panayiota Trifillis, Eugenio Mercuri, Francesco Muntoni, et al.	2023	EPNS23-2064: Age at loss of ambulation in patients with DMD from the STRIDE Registry and the CINRG Natural History Study: a matched cohort analysis	STRIDE VS CINRG	Conf abstract with insufficient detail
C. M. McDonald; F. Muntoni; V. Penematsa; et al.	2022	Ataluren delays loss of ambulation and respiratory decline in nonsense mutation Duchenne muscular dystrophy patients	Study 019 (ataluren) vs CINRG	Small subgroup of CINRG patients matched with ataluren Study 019; Mercuri 2023 CINRG dataset preferred due to larger number of included patients

D. Machado; E. de Paula; T. Márcia; et al.	2022	CO105 Long-Term Benefit of Ataluren Treatment in Non-Sense Duchenne muscular dystrophy Versus Standard of Care	Ataluren (STRIDE vs CINRG and Study 019 vs CINRG)	Conf abstract with insufficient detail
Pannie Trifillis, Francesco Muntoni, Már Tulinius, et al.	2022	P98: Comparison of North Star Ambulatory Assessment score change in nmDMD patients receiving ataluren: STRIDE Registry vs phase 3 clinical trial	STRIDE vs Study 020 NCT01826487	Conf abstract with insufficient detail
E. Mercuri; F. Muntoni; F. Buccella; et al.	2022	P22: Age at loss of ambulation in patients with DMD from the STRIDE registry and the CINRG natural history study: A matched cohort analysis	STRIDE vs CINRG	Conf abstract with insufficient detail
Pannie Trifillis, Eugenio Mercuri, Francesco Muntoni, et al.	2022	P97: Age at loss of ambulation in patients with DMD from the STRIDE Registry and the CINRG Natural History Study: a matched cohort analysis	STRIDE vs CINRG	Conf abstract with insufficient detail
Pannie Trifillis, Már Tulinius, Filippo Buccella, et al.	2022	P99: Pulmonary function in patients with Duchenne muscular dystrophy from the STRIDE Registry and CINRG Natural	STRIDE vs CINRG	Conf abstract with insufficient detail

		History Study: a matched cohort analysis		
Craig McDonald, Claudio L. Santos, Rich Able, et al.	2022	P110: Associations Between Daily Deflazacort or Prednisone and Ages at Disease Progression Milestones Among Patients with Duchenne muscular dystrophy (DMD)	PRO-DMD-01 and CINRG natural history studies	Conf abstract with insufficient detail
M. Tulinius; F. Buccella; I. Desguerre; et al.	2022	P.23 Pulmonary function in patients with Duchenne muscular dystrophy from the STRIDE Registry and CINRG Natural History Study: a matched cohort analysis	STRIDE vs CINRG	Conf abstract with insufficient detail
A. A. Zambon; V. Ayyar Gupta; D. Ridout; et al.	2022	Peak functional ability and age at loss of ambulation in Duchenne muscular dystrophy	UK NorthStar Network	Only ambulation-related outcomes reported; thus Pietrusz subgroup preferred as a consistent set of data reporting both LOA and respiratory outcomes
E. Mercuri; F. Muntoni; A. N. Osorio; et al.	2020	Safety and effectiveness of ataluren: comparison of results from the STRIDE Registry and CINRG DMD Natural History Study	STRIDE vs CINRG	Contains subgroup of dataset reported in Mercuri 2023 that was included in the ITC (STRIDE vs CINRG)

C. M. McDonald; H. Gordish-Dressman; E. K. Henricson; et al.	2018	Longitudinal pulmonary function testing outcome measures in Duchenne muscular dystrophy: Long-term natural history with and without glucocorticoids	CINRG alone (GC > 1 year vs GC naïve)	Outcomes of interest not reported
C. M. McDonald; E. K. Henricson; R. T. Abresch; et al.	2018	Long-term effects of glucocorticoids on function, quality of life, and survival in patients with Duchenne muscular dystrophy: a prospective cohort study	CINRG (NCT 00468832)	Subgroup of CINRG patients reported in Mercuri 2023 preferred as some restrictions applied to the Mercuri dataset, which enabled a more balanced comparison with the givinostat data. For example, 22 CINRG patients were excluded because they had participated in clinical trials of ataluren or had received eteplirsen, drisapersen or tadalafil; 20 patients were also excluded because they had missing data for age at loss of ambulation and age at first symptoms
V. Ricotti; D. A. Ridout; M. Pane; et al.	2016	The NorthStar Ambulatory Assessment in Duchenne muscular dystrophy: considerations for the design of clinical trials	UK NorthStar Network + data from 172 Italian boys with DMD	Outcomes not of interest; no Kaplan-Meier curve for age at LOA

L. Bello; H. Gordish-Dressman; L. P. Morgenroth; et al.	2015	Prednisone/prednisolone and deflazacort regimens in the CINRG Duchenne Natural History Study	CINRG-DNHS	Outcomes not of interest (LOA by steroid regimen for all enrolled CINRG patients)
G. Schram; A. Fournier; H. Leduc; et al.	2013	All-cause mortality and cardiovascular outcomes with prophylactic steroid therapy in Duchenne muscular dystrophy	Retrospective cohort study on patients with DMD treated with renin-angiotensin-aldosterone system antagonists with or without steroid therapy. I think this technically fit the PICOS but didn't really have the key outcomes we were interested in	Outcomes not of interest (mortality and CV events)
V. Ricotti; D. A. Ridout; E. Scott; et al.	2013	Long-term benefits and adverse effects of intermittent versus daily glucocorticoids in boys with Duchenne muscular dystrophy	NorthStar UK database (17 neuromuscular centres in the UK)	Only ambulation-related outcomes considered; thus Pietrusz subgroup preferred as a consistent set of data reporting both LOA and respiratory outcomes and reports more recently collected data, and therefore more likely to reflect current treatment practise
C. M. McDonald; E. K. Henricson; R. T. Abresch; et al.	2013	The 6-minute walk test and other endpoints in Duchenne muscular	The natural history data were derived from the placebo arm of	Short follow-up, 48 weeks only

		dystrophy: longitudinal natural history observations over 48 weeks from a multicenter study	a phase 2b, international, multicenter, randomized, double-blind, placebo-controlled, dose-ranging study to evaluate the efficacy and safety of ataluren in ambulatory male patients aged ≥5 years with nonsense mutation DMD	
E. K. Henricson; R. T. Abresch; A. Cnaan; et al.	2013	The cooperative international neuromuscular research group Duchenne natural history study: glucocorticoid treatment preserves clinically meaningful functional milestones and reduces rate of disease progression as measured by manual muscle testing and other commonly used clinical trial outcome measures	CINRG	No outcomes of interest; short follow-up, 12 months only
G. Stimpson: D. Ridout; A. Sarkozy; A. Manzur; et al.	2024	Relationship between growth and ambulation loss in Duchenne muscular dystrophy boys on steroids	UK NorthStar database	Age at LOA only outcome of interest reported; thus Pietrusz subgroup preferred as a consistent set of data reporting

				both LOA and respiratory outcomes
M. Van Der Holst; M. Italianer; A Wolfe; et al.	2024	Is upper extremity contracture progression related to changes in upper extremity function in Duchenne muscular dystrophy? An international multicenter natural history study	International multicentre natural history study: I think possibly just doesn't have enough of the outcomes needed?	Conf abstract with insufficient detail
V. Laugel; A. Seferian; J.B. Davion; et al.	2024	Preliminary results from a prospective, multicentric, follow up standardized cohort to assess natural history of Duchenne muscular dystrophy	France and UK natural history data (48 patients)	Conf abstract with insufficient detail

Abbreviations: 6MWD, 6-minute walk distance; CINRG, Cooperative International Neuromuscular Research Group; DMD, Duchenne muscular dystrophy; GC, glucocorticoid; MR, magnetic resonance; nm, nonsense mutation; MR, magnetic resonance; NR, not reported; NSAA, North Star Ambulatory Assessment; SLR, systematic literature review; STRIDE, Strategic Targeting of Registries and International Database of Excellence; UK, United Kingdom.

Quality assessment

Relevant data from included clinical studies were inserted into extraction tables in Microsoft Excel®. Data were extracted by one reviewer and spot-checked for quality by a second reviewer; if necessary, discrepancies were reconciled by a third reviewer. When data from multiple publications on the same study cohort were identified, this was captured as a link between the primary and secondary publications.

For quality assessment of RCTs, the Cochrane Risk of Bias (ROB) 2 tool was used. Quality assessment was conducted for each full-length article using the appropriate questionnaires, selected to comply with NICE standard. Conference abstracts were omitted as they are generally judged to be of poor quality using the questionnaires.

Unpublished data

The unpublished data used was not quality assessed.

Appendix I. Literature searches for health-related quality of life

An SLR was conducted to identify relevant published HRQoL evidence in patients with a diagnosis of DMD. The same search was performed for economic evaluations, health-related quality of life (HRQoL), and costs and healthcare resource use (HCRU), as described in Appendix K. Hence, Table 105-Table 107 below are not populated.

Table 105: Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion

Table 106: Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search

Table 107: Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
Conference name				

Search strategies

The search strategy is presented in Appendix K. Hence Table 108 is not populated.

Table 108: Search strategy for [name of database]

No.	Query	Results
#1		
#2		
#3		

No.	Query	Results
#4		
#5		
#6		
#7		
#8		
#9		
#10		

Study selection

Eligibility criteria

The eligibility criteria for HRQoL studies are outlined in Table 109. The same eligibility criteria were used for the update SLR, notwithstanding 'date of publication' which was from the date or the prior SLR to present.

Table 109: HRQoL | Eligibility (PICOS) criteria

	Inclusion criteria	Exclusion criteria
Population	Patients with a diagnosis of DMD or parents/caregivers who provide responses on their behalf (e.g. proxies) Clinicians who manage patients with DMD "Layperson respondents": Individuals who represent the general population*	Other muscular dystrophies including Becker muscular dystrophy
Intervention/ comparator	Any	None
Outcomes	PROs: Utilities derived using generic preference-based instruments (e.g. EQ-5D, SF-6D, HUI2, HUI3) for relevant health states Direct utility estimates (e.g. standard gamble, time trade off, discrete choice experiment) Mapping studies, from disease-specific to generic preference-based measures or between different generic preference-based measures	NA
Study design	Randomised-controlled trials	Non-systematic reviews

	Non randomised-controlled trials Observational studies HRQoL elicitation and validation studies Economic evaluations Economic Evaluation alongside Clinical Trials Health utility studies SLRs of economic evaluations (for reference checking only) Preference research Time trade off Discrete choice experiment	Editorials, comments, letters, case reports, case series Animal studies Individual cost study reports
Language	English only	Non-English
Date of publication	Full publication: No time limit Conference abstract: May 2022 to present	None
Countries	UK, Europe, Canada, Australia or studies that include a UK/EU cohort	None

*Layperson respondents were considered, in case for example, vignette-based exercises using members of the general population were identified as sources of utility estimates.
Abbreviations: DMD, Duchenne muscular dystrophy; EU, European Union; HRQoL, health-related quality of life; HUI, health utilities index; N/A, not applicable; PRO, patient-reported outcome; SF-6D, short-form 6-dimension; SLR, systematic literature review; UK, United Kingdom.

Data extraction and quality assessment

The data extraction process followed the same methodology as detailed in Appendix K.

Results

Literature search results included in the model/analysis

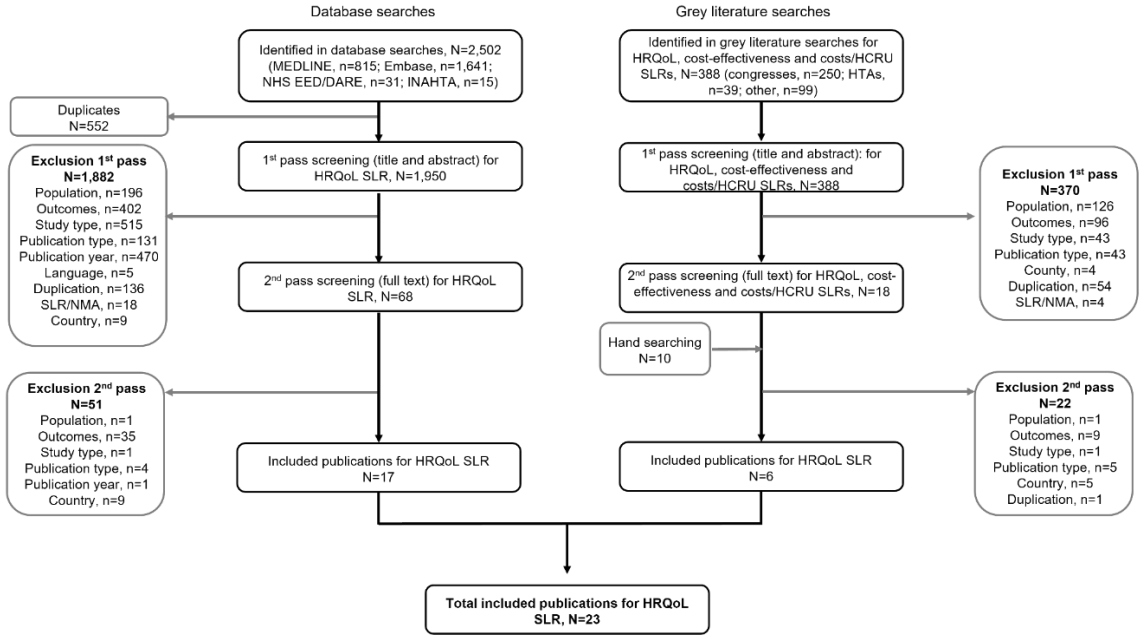
For the original SLR, of the 2,502 papers identified for the cost-effectiveness (Appendix I), HRQoL, and costs and resource use (Appendix K) SLRs by the database searches, 552 were removed as duplicates, and the titles and abstracts of 1,950 papers were reviewed for the HRQoL SLR at first-pass screening. After exclusion of 1,882 papers, the full texts of 68 publications were reviewed at second-pass screening, of which 51 were subsequently excluded. A total of 17 papers met the pre-defined inclusion criteria from the database searches and were included in the HRQoL review.

Of the 388 publications identified by grey literature searching, 370 were excluded following first-pass screening. Additionally, 10 publications were identified through hand searching. Of the 28 publications that were reviewed as full-text articles, 22 were excluded and six met the selection criteria for inclusion in the costs and resource use SLR.

Therefore, a total of 23 publications were included in the HRQoL SLR from the database searches, grey literature searches, and hand searching. The flow of studies through the reviews is reported in the PRISMA flow diagram in Figure 58.

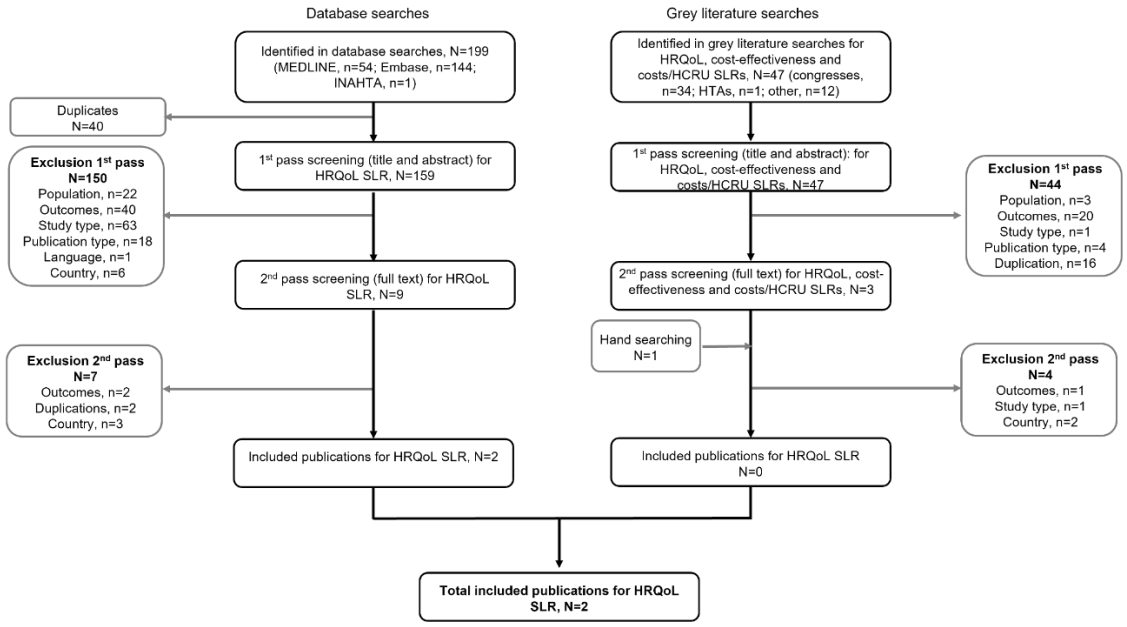
An update of the SLR was run, for the period 07 May 2024 to 07 November 2024, during which two relevant publications were identified. The flow of studies through the reviews is reported in the PRISMA flow diagram in Figure 59.

Figure 58: PRISMA flow diagram for the original HRQoL SLR



Abbreviations: DARE, Database of Abstracts of Reviews of Effects; HCRU, healthcare resource use; HRQoL, health-related quality of life; HTA, health technology assessment; INAHTA; International Health Technology Assessment Database; NHS EED, National Institute for Health Research Economic Evaluation Database; NMA, network meta-analysis; PRISMA, preferred reporting items for systematic reviews and meta-analyses; SLR, systematic literature review

Figure 59: PRISMA flow diagram for the HRQoL SLR update



Abbreviations: HCRU, healthcare resource use; HRQoL, health-related quality of life; HTA, health technology assessment; INAHTA; International Health Technology Assessment Database; PRISMA, preferred reporting items for systematic reviews and meta-analyses; SLR, systematic literature review

Data on HRQoL are sourced from literature. The EQ-5D instrument was not included in the trial program. In EPIDYS trial the PODCI questionnaire was used, in the CEM health states utilities was derived from Audhya et al. (2023b) (Section 10), identified through this SLR.

Table 110 summarises the studies identified reporting EQ-5D data on patient and/or caregiver HRQoL stratified by health state.

Szabo et al. 2023 only report utility values for one health state. Therefore, these data are not considered in the CEM (Szabo et al. 2023a). Castro et al. (2023) and Andreozzi et al. (2022) report utility values based on the Spanish and Portuguese tariffs, respectively . These values appear much lower than other identified studies, with negative values reported for later health states. Therefore, whilst these studies are considered supportive of the inputs informing the CEM - utilities are shown to decline across the progression health states – these studies are not considered in the CEM. However, these studies highlight that the patient utilities informing the CEM may be conservative.

Although the values reported in Crossnohere et al. (2021) are supportive of the outcomes presented in Audhya et al. (2023b) – utilities are shown to decline across the progressing health states and the values reported for the non-ambulatory health states are very similar - these values are not considered within the CEM as HRQoL was proxy-reported by caregivers for patients aged <18. Feedback from clinical experts at the June 2024 advisory board (clinicians in England and Wales) indicated that the perspective is important when assessing patient HRQoL and that values proxy-reported by caregivers would likely differ from self-reported patient values (Italfarmaco 2024b). This is supported by the differing utility values reflecting the three perspectives considered in the study (adult with DMD, caregiver of an adult, and caregiver of a minor). This is further supported by Szabo et al. (2023a) who compare EQ-5D utility values measured by the patient and caregiver for the same health states and find different values depending on perspective.

The values reported in Landfeldt et al. (2017a) are further supportive of the outcomes presented in Audhya et al. (2023b) - utilities are shown to decline across the progressing health states and the values reported are in line with the utilities reported in Audhya et al. (2023b). However, patient utilities were measured using the HUI-3 and proxy-reported by caregivers. Therefore, this is considered unsuitable as a base case but is tested in a scenario analysis as Landfeldt et al. (2017a) was the only study identified which assessed caregiver HRQoL by health state and EQ-5D and is thus considered to inform based case utilities for caregivers. Landfeldt et al. (2017a) estimated utilities using the EQ-5D-3L and the UK value set.

Table 110: Studies assessing utility values in patients with DMD

Citation	Study design	Objective	Countries	Data source	Utilities	Respondents	Mean age	EQ-5D measure
Audhya et al. (2023b). Estimating health state utilities in Duchenne muscular dystrophy using the health utilities index and EQ-5D-5L. Journal of patient-reported outcomes, 7(1), 132. https://doi.org/10.1186/s41687-023-00671-y	Web-based survey	HRQoL impact of DMD	US	Parent Project Muscular Dystrophy, an advocacy group in the US	Patient	N=63 Males with DMD aged 12–40 years	19.8 (6.1)	EQ-5D-5L, US tariff

Szabo et al. (2023a). The Association between Patient-and Caregiver-Reported Utility Values in Duchenne Muscular Dystrophy (DMD) (P31). Value Health, 26(6):S7.	Cross-sectional	Patient- and caregiver-derived utility values for DMD health states	US	US-based patient organization	Patient	N=31 patient-caregiver dyads	14 (5.9)	EQ-5D, level and tariff NR
Castro et al. (2023). Introduction to the Duchenne Muscular Dystrophy Burden-of-Illness Study Expanded (US AND SPAIN) EE92. Value Health, 26(12):S68.	Cross-sectional	Interim analysis from PH BOI study in US and Spain	US and Spain	Male patients diagnosed with DMD at least 12 months before date of consultation (index date), prospectively recruited by neuromuscular physicians in specialist DMD centres	Patient	N=56 Caregiver and patient (for patients with cognitive delay or below 16 years, caregivers were asked to complete the study on the patient's behalf)	16.9 (8.8)	EQ-5D-5L, Spanish tariff
Andreozzi et al. (2022). Quality of life and informal care burden associated with duchenne muscular dystrophy in Portugal: the COIDUCH study. Health and quality of life outcomes, 20(1), 36.	Cross-sectional	HRQoL of DMD patients	Portugal	Portuguese Neuromuscular Association	Patient	N=46 caregivers	18.9± 8.2	EQ-5D-3L, Portuguese tariff
Crossnohere et al. (2021). Assessing the Appropriateness of the EQ-5D for Duchenne Muscular Dystrophy: A Patient-Centered Study. Med Decis Making, 41, 209-221.	Cross-sectional	Assess the appropriateness of the EQ-5D in DMD	Australia, Belgium, Canada, Netherlands, UK, US	International patient advocacy groups	Patient	N=61 adults with DMD Males ≥18-years with DMD	28.2 (18-48)	EQ-5D-3L, US tariff
						N=134 Caregivers ≥18-years of a male <18-	42.4 (23-65)	EQ-5D-3L, US tariff

						years with DMD		
						N=68 Caregivers ≥18-years of a male ≥18-years with DMD	54.9 (40–70)	EQ-5D-3L, US tariff
Landfeldt et al. (2016b). Quantifying the burden of caregiving in Duchenne muscular dystrophy. J Neurol, 263, 906-915. Landfeldt et al. (2017a). Economic Evaluation in Duchenne Muscular Dystrophy: Model Frameworks for Cost-Effectiveness Analysis. Pharmacoeconomics, 35, 249-258.	Cross-sectional	Burden among caregivers of patients with DMD	Germany, Italy, UK, US	TREAT-NMD	Caregivers	Caregivers of males with DMD aged ≥ 5 years	44 (39–50)	EQ-5D, UK tariff

Abbreviations: BOI: burden of illness; DMD: Duchenne muscular dystrophy; EQ-5D: EuroQol 5-dimensions; HRQoL: health-related quality of life; NR: not reported.

Quality assessment and generalizability of estimates

The data extraction process followed the same methodology as detailed in Appendix H.

Unpublished data

Not applicable.

Excluded studies

Overall, 2,325 papers were excluded during first-pass and full-text screening in the original HRQoL SLR. Through database searches, 1,882 papers were excluded during first-pass screening and 51 were excluded during full-text screening. Through grey literature searches, 370 publications were excluded during first-pass screening and 22 were excluded during full-text screening. One study that was initially excluded based on country of data source was included during the SLR update.

For the SLR update, a total of 205 publications were excluded; for the database searches 150 were excluded during first-pass screening and seven during second-pass screening and for the grey literature searches 44 were excluded during first-pass screening and four during second-pass screening.

Due to the large number of studies excluded, these are attached as separate files (Italfarmaco 2024o, Italfarmaco 2024p, Italfarmaco 2024q, Italfarmaco 2024r, Italfarmaco 2024m, Italfarmaco 2024n).

Outcomes of included publications

Table 111 presents the summary of outcomes for the 25 identified publications.

Table 111: Summary of results of the included HRQoL studies

Author. Year Source publication	Population and sample size (or reference/source) Recruitment	Utilities	Details of utilities					Description of health states
			Reported by	n	Measure	Intervention utilities	Comparator utilities	
Szabo et al. (2023a)	31 Patient-caregiver dyads were recruited through a US-based patient organisation	Patient	Caregiver and patient	31	EQ-5D VAS HUI	Median (IQR) Patient-reported example given: non-ambulatory patients with mildly impaired upper limb function, without night-time/ daytime ventilation or symptomatic cardiomyopathy (n=7) were: EQ-5D: 0.30 (0.24-0.35;) HUI2: 0.51 (0.44-0.52) VAS: 84 (74-96)	Median (IQR) Caregiver reported example given: non-ambulatory patients with mildly impaired upper limb function, without night-time/ daytime ventilation or symptomatic cardiomyopathy (n=7) were: EQ-5D: 0.15 (0.07-0.18) HUI2: 0.47 (0.47-0.55) VAS: 80 (75-87)	Patients were classified into one of nine DMD-related health states according to level of lower/upper limb function, daytime/night-time ventilation, and cardiomyopathy

						Across health states, caregivers reported lower EQ-5D (p,0.001) and VAS (p=0.04) values than patients; HUI2 utilities did not differ by respondent type	
Szabo et al. (2023b)	English speaking individuals with DMD <40 years or caregivers reporting on their behalf, who lived in the US and participated in a previous study Parent Project Muscular Dystrophy (PPMD)'s Duchenne Registry, facilitated recruitment for this study.	Patient	Caregiver and patient	47	EQ-5D HUI	Mean (SD) EQ-5D: 0.40 (0.32) HUI2: 0.61 (0.21) HUI3: 0.39 (0.31)	NR
Audhya et al. (2023b)	Male individuals with DMD in the US aged 12–40 years. Participants were recruited through	Patient	Patient Participants were advised they could ask their parent to help them to	63	HUI2 HUI3 EQ-5D-5L (only EQ-5D data extracted)	**Mean EQ-5D-5L (SD)** • EA (n=11): 0.79 (0.20) – Preserved upper limb function, no daytime ventilation, without symptomatic CM (n=10): 0.84 (0.13)	Health states based on primary and secondary manifestations relevant to the natural history of DMD.

Parent Project Muscular Dystrophy.	complete the survey		– Mildly impaired upper limb function, no daytime ventilation, without symptomatic CM (n=1): 0.30 (NA) • LA (n=8): 0.64 (0.30) – Transitional, preserved upper limb, no daytime ventilation, without symptomatic CM (n=6): 0.59 (0.33) – Transitional, mildly impaired upper limb, no daytime ventilation, without symptomatic CM (n=2): 0.79 (0.16) • ENA (n=21): 0.31 (0.13) – Preserved upper limb function, no daytime ventilation, without symptomatic CM (n=2): 0.46 (0.10) – Mildly impaired upper limb function, no daytime ventilation, without symptomatic CM (n=16): 0.30 (0.14) – Mildly impaired upper limb function, no daytime ventilation, with symptomatic CM (n=3): 0.29 (0.07) • LNA (n=23): 0.22 (0.15) – Moderately impaired upper limb function, no daytime ventilation, without symptomatic CM (n=9): 0.22 (0.15)	Primary manifestations: • EA • LA • ENA • LNA Each primary manifestation was subdivided by the presence or absence of secondary manifestations: • Upper limb function – Preserved – Mildly impaired – Moderatly impaired – Loss of function • Respiratory support – No daytime ventilation

						– Moderately impaired upper limb function, no daytime ventilation, with symptomatic CM (n=4): 0.27 (0.08) – Moderately impaired upper limb function, daytime and nighttime ventilation, without symptomatic CM (n=5): 0.25 (0.14) – Loss of upper limb function, no daytime ventilation, without symptomatic CM (n=1): 0.26 (NA) – Loss of upper limb function, daytime and nighttime ventilation, without symptomatic CM (n=2): 0.26 (0.01) – Loss of upper limb function, daytime and nighttime ventilation, with symptomatic CM (n=2): 0.02 (0.34)	– Nighttime and daytime ventilation • Cardiomyopathy – Without symptomatic CM – With symptomatic CM
Audhya et al. (2023a)	Ambulant males aged ≥5 years with DMD Data from placebo-treated ambulant males with DMD with exon 51 skip amenable	Patient	Caregiver	61	HUI	At baseline, the mean (SD) utility score was 0.82 (0.19) for the HUI3 and 0.87 (0.13) for the HUI2. The mean (SD) NSAA total score was 21.0 (8.1).	Utilities were correlated with NSAA scores (score range, 0 to 34)

	mutations recruited under NCT01254019 (provided by Biomarin Pharmaceutical Inc.) were included.					Weak positive correlations were observed between NSAA scores and HUI scores at baseline (HUI3: r=0.17; HUI2: r=0.29). HUI scores decreased over time, with a mean (SD) utility score at week 48 (or early withdrawal) of 0.75 (0.22) for the HUI3 and 0.81 (0.18) for the HUI2. This was a decrease of 0.06 (0.19) and 0.05 (0.14), respectively. NSAA scores also decreased over time to a mean NSAA score of 18.3 (10.1) at week 48, reflecting a decrease of 2.9 (4.7) from baseline. Weak positive correlations were observed between the change in NSAA scores and HUI scores over 48 weeks (HUI3: r=0.15; HUI2: r=0.16). A one-unit decline in NSAA score was associated with a 0.010 decline in HUI3 utility and a 0.004 decline in HUI2 utility.	
Castro et al. (2023)	Male patients diagnosed with DMD (via muscle biopsy or genetic test) at least 12 months before date of consultation (index date), prospectively	Patient	Caregiver and patient (for patients with cognitive delay or below 16 years,	56	EQ-5D-5L utility scores were calculated using Spanish value sets	Mean EQ-5D-5L utility scores decreased as DMD severity progressed Disease stage 1: 0.60 Disease stage 2: 0.62	NR

	recruited by neuromuscular physicians in specialist DMD centres during regular consultation		caregivers were asked to complete the study on the patient's behalf)		as they were available for all versions of the EQ-5D	Disease stage 3: 0.58 Disease stage 4: 0.39 Disease stage 5: 0.27 Disease stage 6: 0.06 Disease stage 7: -0.02 Disease stage 8: -0.39	
Jurikova, 2023	Patients with DMD, participants of a survey	Patient	Caregiver	63	EQ-5D Utility index	The EQ-5D Utility Index decreased from 0.712 in children under 5 years to 0.026 in 18+years group	NR
Muntoni et al. (2023)	Boys with DMD Placebo arm data from phase 3 clinical trials and RW registries	Patient	NR	1.175	HUI	EA (953 patients): 0.83 ± 0.02 LA (406 patients): 0.77 ± 0.04 Transfer (37 patients): 0.48 ± –	State 1: EA: Able to rise from supine; Able to walk 10 meters State 2: LA: not able to rise from supine; Able to walk 10 meters State 3: Transfer: not able to rise from supine; not able to walk 10 meters; able to remain standing

								State 4: HTMF, no ventilation: PUL entry item ≥2; FVC%p ≥50% State 5: No HTMF, no ventilation: PUL entry item <2; FVC%p ≥50% State 6: HTMF, night-time ventilation: PUL entry item ≥2; 30% ≤FVC%p <50% State 7: No HTMF, night-time ventilation: PUL entry item <2; 30% ≤FVC%p <50% State 8: Full-time ventilation: PUL entry item <2; FVC%p <30%
NICE (2023a)	DMD Delphi panel study (Landfeldt et al. 2020)	Patient	Neuro/ muscular experts	6	HUI3	Ataluren: 0.93	Best supportive care: 0.62	NR

Landfeldt et al. (2022)	Delphi panel comprising of physicians with first-hand experience of ataluren for the treatment of nmDMD	Patient	Delphi panel	9	Consensus HUI-derived utilities	Consensus HUI-derived utilities for ataluren + BSC: Stage (1): 1.0000 Stage (2): 0.3179 Stage (3): 0.1643 Stage (4): -0.0732	Consensus HUI-derived utilities for BSC: Stage (1): 0.7337 Stage (2): 0.2672 Stage (3): 0.0913 Stage (4): -0.1163	Four disease stages: (1) ambulatory (patient age: 10 years) (2) non-ambulatory, not yet requiring ventilation support (3) non-ambulatory, at the time of initiation of night-time ventilation support (4) non-ambulatory, at the time of initiation of full-time ventilation support
Szabo et al. (2022)	Ambulant boys with DMD aged ≥5 years, with exon 51 skip amenable mutations, randomized to the placebo arm of the DEMAND trial (NCT01254019; provided by BioMarin Pharmaceuticals Inclusion criteria	Patient	Caregiver	61	HUI, HUI2, HUI3	Baseline, mean (SD) Overall: HUI3: 0.82 (0.19) HUI2: 0.87 (0.13) Boys aged 5 to <8: HUI3: 0.82 (0.20), n = 28		NR

	required participants be able to complete the six minute walk distance (6MWD) of ≥75 m at each pre-drug visit	HUI2: 0.87 (0.15), n = 27 Boys aged 8–16: HUI3: 0.82 (0.19), n = 32 HUI2: 0.86 (0.12), n = 31 At 24 weeks, mean (SD) Boys aged 5 to <8: HUI3: 0.78 (0.27) HUI2: 0.86 (0.15) Boys aged 8–16: HUI3: 0.76 (0.23) HUI2: 0.82 (0.15) At 48 weeks, mean (SD) Overall: HUI3: 0.75 (0.22) HUI2: 0.81 (0.18) HUI3 utility change: -0.06 (0.19)

						HUI2 utility change: -0.05 (0.14) Mean utility having declined more among the older boys than the younger boys Boys aged 5 to <8 HUI3: 0.80 (0.19), n = 28 HUI2: 0.84 (0.17), n = 28 Boys aged 8–16: HUI3: 0.71 (0.23), n = 30 HUI2: 0.77 (0.18), n = 29		
Landfeldt, 2022	Nine neuromuscular specialists, adult and paediatric neurologists, and paediatricians from five countries. Clinical experts were identified from specialist/tertiary centres across Europe. Inclusion criteria were acting as the coordinating/specialist	Patient	Clinical experts	9	HUI	Consensus HUI-derived utilities: Stage 1, ambulatory: 1.0000 Stage 2, non-ambulatory, not yet requiring ventilation support: 0.3179 Stage 3, non-ambulatory, requiring night-time	Consensus HUI-derived utilities: Stage 1, ambulatory: 0.7337 Stage 2, non-ambulatory, not yet requiring ventilation support: 0.2672 Stage 3, non-ambulatory, requiring night-time	Health states defined by ambulatory vs. non-ambulatory status

	physician to patients with DMD and first-hand experience with ataluren for the treatment of nonsense mutation DMD. 14 panellists were invited and 9 responded (response rate: 64%).					ventilation support: 0.1643 Stage 4, non-ambulatory, requiring full-time ventilation support: -0.0732 Consensus VAS scores: Stage 1: 80 Stage 2: 61 Stage 3: 55 Stage 4: 46	ventilation support: 0.0913 Stage 4, non-ambulatory, requiring full-time ventilation support: -0.1163 Consensus VAS scores: Stage 1: 62 Stage 2: 56 Stage 3: 46 Stage 4: 38
Audhya, 2022	8 patients with DMD and 26 caregivers. Members of the US general public were recruited from a market research panel, online advertising, and social media	Patient	Caregiver and patient, plus clinicians + US general public	190	Time trade-off utility value	Mean (SD) utility values: Preserved/mildly impaired ambulatory function: 0.74 (0.29) Moderately/severely impaired Ambulatory function: 0.65 (0.33)	Preserved/mildly impaired ambulatory function Moderately/ severely impaired ambulatory function

						Non-ambulatory with preserved/mildly Impaired upper limb function and non-invasive ventilation: 0.48 (0.34) Non-ambulatory with severe loss of upper limb function and non-invasive ventilation: 0.27 (0.31)	Non-ambulatory with preserved/mildly impaired upper limb function and non-invasive ventilation Non-ambulatory with severe loss of upper limb function and non-invasive ventilation
Andreozzi, 2022	Patients with DMD and their main caregivers, identified through Portuguese Neuromuscular Association (APN).	Patient	Caregiver	46	EQ-5D-3L proxy version	Overall, DMD patients had a low HRQoL, with a mean utility value of 0.05 (SD, 0.33). The presence of negative utility values was higher among non-ambulant patients (61%), with a mean utility value of −0.05 (SD, 0.24), while entirely absent in ambulant patients, which had a mean utility value of 0.51 (SD, 0.28). The difference in utility values according to ambulatory status was statistically significant (p<0.001). Patients with full-time ventilation support presented the lowest mean utility value (−0.20; SD, 0.22), followed by patients with non-full-time ventilation support (−0.05; SD, 0.21) and no ventilation support (0.03; SD, 0.29). Although data suggest a decline of HRQoL utility values while the need for	Utilities reported for health states based on ambulatory vs. non-ambulatory status and level of need for ventilation support

						ventilation support increases, statistical significance was not reached (p=0.228). The presence of negative utilities was higher in full-time (86%) and non-full-time ventilated (60%) patients, slightly less so in patients with no ventilation support (45%). There were, however, no statistically significant difference between groups (p=0.233).	
SMC2327	Landfeldt et al. 2017	Patient	NR	NR	HUI3	The proportional decrement applied for non-ambulatory (predicted FVC>50%) resulted in higher utility for ataluren in this impaired state than for ambulatory best supportive care. The submitting company assigned full per person utility estimates to each caregiver (two caregivers assumed), rather than utility decrements, and attributed further gains to ataluren based on delayed bereavement, assuming a fixed life year gain of five, with 9% of this (0.45), taken as being the bereaved persons' QALY loss.	NR
Crossnohere 2021	Adults with DMD (n=61)	Patient	Caregiver and patients	263	EQ-5D-3L EQ-VAS	Mean (SD) EQ-5D-3L index score and mean (SD) VAS score:	Health states defined by ambulatory vs. non-ambulatory status

	Caregivers of minor (n=134)	PUL-PROM	Patient aged 9 or younger (n=62): 0.59 (0.21) and 71 (14)
	Caregivers of adult (n=68)		Patient aged 10-19 (n=94): 0.42 (0.25) and 65 (18)
	Individuals identified through advocacy groups		Patient aged 20-29 (n=69): 0.33 (0.21) and 65 (23)
			Patient aged 30-39 (n=31): 0.26 (0.16) and 61 (24)
			Patient age 40+ (n=7): 0.27 (0.16) and NR
			Adult with DMD (n=61): 0.40 (0.19) and 74 (20)
			Caregiver of adult (n=68): 0.27 (0.20) and 55 (22)
			Caregiver of minor (n=134): 0.50 (0.25) and 68 (16)
			EA (n=71): 0.65 (0.17) and 73 (14)
			LA (n=31): 0.49 (0.23) and 62 (17)
			ENA (n=111): 0.31 (0.20) and 65 (20)
			LNA (n=50): 0.26 (0.16) and 60 (25)

PUL-PROM

PUL-PROM lower 25th percentile, 0-11 (n=66): 0.24 (0.17) and 63 (25)

PUL-PROM 26th-50th percentile, 12-40 (n=62): 0.31 (0.18) and 64 (20)

PUL-PROM 51st-75th percentile, 41-54 (n=62): 0.51 (0.23) and 69 (14)

PUL-PROM 76th-100th percentile, 55-64 (n=56): 0.62 (0.19) and 69 (17)

Optimistic, yes (n=185): 0.43 (0.25) and 69 (19)

Optimistic, no (n=78): 0.37 (0.24) and 60 (22)

Self-control, yes (n=210): 0.43 (0.25) and 67 (20)

Self-control, no (n=53): 0.38 (0.24) and 64 (20)

Health seeking, yes (n=203): 0.42 (0.25) and 67 (20)

						Health seeking, no (n=60): 0.39 (0.24) and 65 (21) Risk taking, yes (n=104): 0.41 (0.25) and 65 (20) Risk taking, no (n=158): 0.41 (0.41) and 67 (20) Comfortable with numbers, yes (n=180): 0.43 (0.24) and 65 (20) Comfortable with numbers, no (n=82): 0.38 (0.26) and 68 (21) Index scores of ambulatory patients were significantly higher than those for non-ambulatory patients, 0.60 (95% CI, 0.56 to 0.64) vs. 0.30 (95% CI, 0.26 to 0.32) (p<0.001). This relationship held even after adjusting for patient age (p=0.001) and respondent role (p=0.001) in regression-based sensitivity analysis. There were no differences in VAS scores across the binary measure of ambulatory status (p>0.05).	
Rowen, 2021	Respondents were recruited using an existing online panel	Patient	Discrete choice experiment	1,043	DMD-QoL	Utility values for each health state are generated by adding the sum of the utility decrements to 1. The best state defined by	A health state classification system was derived from the

	from a market research agency, and quotas were set for age and sex to ensure a representative sample of the UK population in terms of age and sex according to the 2011 UK census. Members of the online panel received an invite to the survey in their agency portal and the survey remained open until all combined age and sex quotas for a sample size of 1,000 were met.		survey respondents			the classification system has a value of 1 and the worst state has a value of -0.559.	DMD-QoL based on psychometric performance of items, factor analysis, and item response theory analysis. Preferences for health states described by the classification system were elicited using an online discrete choice experiment survey with life years as an additional attribute, from members of the UK general population. The health state classification system has 8 dimensions: mobility, difficulty using hands, difficulty breathing, pain, tiredness, worry, participation, and feeling good about yourself.
Landfeldt, 2017	Patient utilities: based on preference data collected using the	Patient	Caregiver	NR	HUI3	Mean (SD)	Model I: total of 25 states, one for each DMDSAT score and an

Landfeldt E. Neurology. 2014;83:529–36. Landfeldt E. Dev Med Child Neurol. 2016;58(5):508–15. Landfeldt E. J Neurol. 2016;263(5):906–15.	standard gamble method and a visual analogue scale from 256 randomly selected members of the general population in Canada					Model I (DMDSAT): initial score, 0.879 (0.037); per lost score, 0.905 (1.003) Model II (ambulatory status): EA, 0.699 (0.036); LA, 0.607 (0.029); ENA, 0.224 (0.014); LNA, 0.146 (0.010) Model III (ventilation status): none, 0.518 (0.027); night-time, 0.129 (0.017); day- and night-time, 0.051 (0.010)	absorbing state for dead Model II: five states: (1) EA (approximately age 5–7 years); (2) LA (approximately age 8–11 years); (3) ENA (approximately age 12–15 years); (4) ENA (approximately age 16 years or older); and (5) an absorbing state for dead
	Caregiver utilities: EQ-5D-3L utilities were derived using the UK value set, which is based on preference data collected through the time-trade off method from 2,997 randomly selected members of the non-institutionalised adult general population in England, Scotland and Wales	Caregiver	Caregiver	NR	EQ-5D-3L	Mean (SD) Model I (DMDSAT): initial score, 0.862 (0.016); per lost score, 0.995 (1.001) Model II (ambulatory status): EA, 0.858 (0.017); LA, 0.839 (0.017); ENA, 0.784 (0.021); LNA, 0.810 (0.018) Model III (ventilation status): none, 0.837 (0.014); night-time, 0.775 (0.030); day- and night-time, 0.774 (0.033)	Model III: four states: (1) no ventilation support; (2) night-time ventilation support; (3) day- and night-time ventilation support; and (4) an absorbing state for dead In each model, every cycle, patients had a probability of remaining in the current state,

								progressing to a more severe state, or dying
Hind, 2017	Population: ambulant boys aged 7–16 years with genetically confirmed DMD, NSAA score of ≥8, established on corticosteroid therapy, that is, a patient has been treated with prednisolone or deflazacort for at least 6 months with no major change in drug, dosage or frequency for at least 3 months before the initial assessment. Sample size: N=12; intervention, n=8; control, n=4 Participants of a randomised-controlled study	Patient	Caregiver	Intervention n=8 Control n=3 at baseline n=1 at 6 months	CHU	Baseline: Mean (SD), 0.77 (0.223) Median (IQR), 0.88 (0.59–0.94) Min–max, 0.39–0.96 6 months: Mean (SD), 0.87 (0.09) Median (IQR), 0.87 (0.82–0.95) Min–max, 0.71–1	Baseline: Mean (SD), 0.92 (0.07) Median (IQR), 0.89 (0.87–1) Min–max, 0.87–1 6 months: Mean (SD), 0.95 (N/A) Median (IQR), 0.95 (0.95–0.95) Min–max, 0.95–0.95	NR
		Caregiver	Caregiver	Intervention n=7 Control	CarerQol score	Baseline: Mean (SD), 40.6 (22.9) Median (IQR), 29.3 (24.4–59.4)	Baseline: Mean (SD), 31.27 (10.37) Median (IQR), 26.2 (24.4–43.2)	

				n=3 at baseline n=1 at 6 months		Min–max, 19.7–81.6 6 months: Mean (SD), 51.27 (6.78) Median (IQR), 50.1 (48.8–50.4) Min–max, 44–65.8	Min–max, 24.4–43.2 6 months: Mean (SD), 50.1 (N/A) Median (IQR), 50.1 (50.1–50.1) Min–max, 50.1–50.1
Landfeldt, 2016	Caregivers to patients with DMD Recruited through national DMD registries which form part of the global TREAT-NMD network	Caregiver	Caregiver	770	EQ-5D	EQ-5D The sex- and age-matched loss in caregiver utility in relation to the general population was estimated at between: Across ambulatory classes: 0.09 (95 % CI 0.07–0.11) and 0.14 (0.11–0.17) Across caregivers' rating of their sons' current health: 0.06 (0.04–0.07) and 0.18 (0.13–0.23) Across caregivers' rating of their sons' current mental status: 0.09 (0.07–0.10) and 0.30 (0.13–0.46) Mean EQ-5D utility by ambulatory status	NR

EA (n=155): 0.85

LA (n=256): 0.83

ENA (n=154): 0.77

LNA (n=205): 0.79

Mean EQ-5D utility by caregivers' rating of their sons' current health:

Excellent (n=145): 0.88

Very good (n=321): 0.83

Good (n=228): 0.77

Fair/Poor (n=76): 0.71

Mean EQ-5D utility by caregivers' rating of their sons' current mental status:

Hapy and interested in life (n = 455): 0.84

Somewhat happy (n=239): 0.79

Somewhat unhappy (n=63): 0.69

Very unhappy (n=13): 0.57

VAS

Mean VAS scores was lower than the estimated EQ-5D utilities in all strata, except for caregivers to patients rated to be very unhappy. Neither mean utilities nor VAS scores were significantly different across countries.

Mean VAS score by ambulatory status

EA (n=155): 0.76

LA (n=256): 0.75

ENA (n=154): 0.71

LNA (n=205): 0.74

Mean VAS score by caregivers' rating of their sons' current health:

Excellent (n=145): 0.80

Very good (n=321): 0.76

Good (n=228): 0.71

Fair/Poor (n=76): 0.61

						Mean VAS score by caregivers' rating of their sons' current mental status: Happy and interested in life (n = 455): 0.77 Somewhat happy (n=239): 0.72 Somewhat unhappy (n=63): 0.65 Very unhappy (n=13): 0.58	
Landfeldt, 2016	Patient-caregiver pairs Patients were identified through national DMD registries that form part of the global TREAT-NMD Neuromuscular Network.	Patient	Caregiver and patient	770 (192 from the UK)	HUI PedsQL	HUI-derived utilities representing public preferences, over the course of disease progression, ranged from 0.75 in EA patients to 0.15 in LNA patients (p<0.001). Mean HUI-derived utility was significantly associated with the caregivers' rating of their patients' current health (p<0.001), and current mental status (p<0.001). HUI-estimates were comparable across countries (p=0.165). Caregiver proxy-assessed PedsQL total scores were significantly associated with ambulatory class (mean score range 52–72, p<0.001) and significantly associated with the caregivers' rating of their patients' current health (mean score range 26–73, p<0.001) and current mental status (mean score range 43–67, p<0.001). The mean HUI-derived utility and PedsQL total score in patients requiring ventilation support was	Health states defined by ambulatory vs. non-ambulatory status

						estimated at 0.10 and 48, respectively. Across countries, proxy-assessed mean PedsQL total scores ranged between 58 and 65 (p=0.001). A total of 518 (67%) patients (mean age 15 y, range 5–43 y) were able to complete the PedsQL without help from their caregivers. The mean self-assessed PedsQL total score was estimated to be between 57 and 80 across ambulatory classes (p<0.001), between 26 and 76 across the caregivers' rating of their patients' current health (p<0.001), and between 50 and 73 across the caregivers' rating of their patients' current mental status (p<0.001). The mean score in patients requiring ventilation support was 52. Patients' self-assessed PedsQL total scores were consistently higher than caregivers' proxy-assessed scores across the investigated strata.	
Cavazza, 2016	Patients with DMD, recruited by patient organisations, and caregivers	Patient	NR	18 (in the UK)	EQ-5D EQ-VAS Barthel index	Mean (SD) utilities, adult patients: -0.08 (0.07) Mean (SD) VAS, adult patients: 55.6 (24.2) Mean (SD) Barthel index, patients: 6.6 (2.2)	NR

		Caregiver	Caregiver	10 (in the UK)	EQ-5D	Mean (SD) utilities: 0.72 (0.37)	
					EQ-VAS	Mean (SD) VAS: 81.5 (16.5)	
					Zarit scale	Mean (SD) Zarit scale: 31.3 (12.3)	
Landfeldt, 2015 Landfeldt E. Neurology 2014;83:529–36. Landfeldt E. Dev Med Child Neurol 2015;doi:10.1111/dmcn.12938. Landfeldt E, Neuromuscul Dis 2015;2:63–72.	186 patient-caregiver pairs. Patients with DMD were identified through the Translational Research in Europe–Assessment and Treatment of Neuromuscular Diseases (TREAT-NMD) network.	Patient	Caregiver and patient	186	DMDSAT	The total DMDSAT score ranged from 0 (low functional ability) to 23 (high functional ability). Mean (SE) initial utility score (full functional ability): 0.879 (0.037) Mean (SE) utility per lost DMDSAT score (multiplier): 0.905 (1.003) The mean loss in patient utility per one-point change in DMDSAT total scare was 9.5% (95% CI, 9.0% to 10.1%, p<0.001). Spearman's p between predicted and observed patient utility was estimated at 0.85 (p<0.001).	The total DMDSAT score ranged from 0 (low functional ability) to 23 (high functional ability).
		Caregiver	Caregiver and patient	186	DMDSAT	Mean (SE) initial utility score (full functional ability): 0.862 (0.016) Mean (SE) utility per lost DMDSAT score (multiplier): 0.995 (1.001)	

Pangalila, 2012 Hoeymans N, Qual Life Res 2005;14: 655–663.	Parents of adult, severely disabled patients with DMD. Patients were recruited by all four Centres for Home Ventilation in the Netherlands, and by Dutch rehabilitation centres and the Dutch patient organisation for neuromuscular diseases (Vereniging Spierziekten Nederland [VSN]).	Patient	NR	57	EQ-5D HADS	The health status of the patients, measured by the index value score of the EQ-5D was low (mean 0.44; general population mean 0.87). On the HADS anxiety scale (mean 5.3, SD 3.6), 21% of the patients scored in the intermediate range (8–11) and 5 % in the clinical range (12+); on the Depression Scale (mean 5.2, SD 2.7) 22% scored in the intermediate range (8–11) and 2% in the clinical range (12+).	NR
		Caregiver	Caregiver	80	EQ-5D HADS CSI SRB CarerQoL VAS	For parents, the mean health status (0.87) according to the index value score of the EQ-5D was comparable that of the general Dutch population. On the HADS anxiety scale (mean 6.3, SD 4.0) 21% of parents scored in the intermediate range and 12% in the clinical range. On the Depression Scale (mean 5.7, SD 2.8), 19% of parents scored in the intermediate range and 5% in the clinical range. The mean unweighted subjective burden level (6.8, SD 2.8) measured with the CSI and the mean weighted burden level (5.4, SD 2.8) measured with the Self-Rated Burden Scale (SRB) demonstrate that many parents of adult men with DMD experience substantial burden. 32 out of 80 parents had a CSI score	

						of 7 or higher, the cut-off value for substantial burden. Their mean happiness score (CarerQoL VAS) was 7.4 (SD 1.5).	
De Waele, 2024	Patients were enrolled at University Hospital Leuven. Electronic case record forms were obtained for 25 patients, of whom 21 patients completed the patient survey, of whom 16 completed the EQ-5D-5L and 17 completed the DMDQoL.	Patient	Patient	25	EQ-5D-5L DMDQoL	Mean (SD) EQ-5D-5L index score (n=16): 0.27 (0.21) Mean (SD) DMDQoL index score (n=17): 0.61 (0.18)	Disease stage defined by the Project HERCULES natural history of disease model. Patients were classified as disease stage 1 (n=7), 2 (n=1), 4 (n=7), 5 (n=2), 6 (n=1), 7 (n=5), 8 (n=2).
Muntoni, 2024	The study used data from nine sources (clinical trial placebo arms as well as real-world and natural history datasets). The study included 1,173 patients with DMD across 5,306 visits.	Patient	NR	1,173	Health utility index	Mean (SE) health utility index 0.83 (0.02) in early ambulatory stage (n=951) 0.77 (0.04) in late ambulatory stage (n=403) 0.67 (0.13) in transfer stage (n=50) NR for other disease stages	Disease stage defined by the Project HERCULES natural history model of disease progression.

Abbreviations: 6MWD, six meter walking distance; BSC, best supportive care; CHU, child health utility; CM, cardiomyopathy; CSI, caregiver strain index; DMD, Duchenne muscular dystrophy; DMDSAT, Duchenne muscular dystrophy Self-Assessment Tool; EA, early ambulatory; ENA, early non-ambulatory; FVC, forced vital capacity; HADS, hospital anxiety and depression scale; HRQoL, health-related quality of life; HST, highly specialised technology; HTMF, hand-to-mouth function; HUI, health utility index; IQR, interquartile range; LA, late ambulatory; LNA, late non-ambulatory; NICE, National

Institute for Health and Care Excellence; nm, nonsense mutation; NR, not reported; NSAA, north star assessment; Peds-QL, paediatric quality of life; PUL, performance of upper limb; PUL-PROM, Performance of the Upper Limb Patient-Reported Outcome Measure; QALY, quality adjusted life year; QoL, quality of life; RW, real world; SD, standard deviation; SE, standard error; SMC, Scottish Medicine Consortium; SRB, Self-Rated Burden Scale; UK, United Kingdom; VAS, visual analogue scale, US, United States

Critical appraisal for each study

Refer to Appendix K for the quality assessment of the included studies in the cost-effectiveness (Appendix K), HRQoL (Appendix I), and costs and resource use SLRs (Appendix J).

Appendix J. Literature searches for input to the health economic model

External literature for input to the health economic model

Systematic search for economic evaluations, health-related quality of life, costs and healthcare resource use

An SLR was conducted to identify relevant published evidence of the costs and healthcare resource use of DMD. The same search was performed for economic evaluations, health-related quality of life (HRQoL), and costs and healthcare resource use (HCRU), as described in Appendix K. Hence, Table 112 is not populated.

Table 112 Sources included in the search

Database	Platform/source	Relevant period for the search	Date of search completion

Abbreviations:

Eligibility criteria

The eligibility criteria for the costs and HCRU SLR are outlined in Table 113. The same eligibility criteria were used for the update SLR, notwithstanding 'date of publication' which was from the date or the prior SLR to present.

Table 113: Costs and HCRU SLR | Eligibility (PICOS) criteria

	Inclusion criteria	Exclusion criteria
Population	Patients with a diagnosis of DMD	Other muscular dystrophies including Becker muscular dystrophy
Intervention/ comparator	Any	None

Outcomes	• Cost estimates • Direct medical costs including but not limited to treatment cost/administration cost and cost for managing adverse events • Direct non-medical costs • Indirect/societal costs • Patient, caregiver, family, and societal burden including but not limited to: • Out-of-pocket costs expenses • Estimates of resource use • Cost drivers	N/A
Study design	Any, including but not limited to: • CEA • CUA • CMA • CCA • CBA • COA • Budget impact analysis • Burden of illness studies • Resource use studies	• Non-systematic reviews • Editorials, comments, letters, case reports, case series • Animal studies
Language	English only	Non-English
Date of publication	Full publication: 2014 to present Conference abstract: May 2022 to present	None
Countries	UK, Europe, Canada, Australia or studies that include a UK/EU cohort	None

Abbreviations: CBA, cost-benefit analysis; CCA, cost-consequence analysis; CEA, cost-effectiveness analysis; CMA, cost-minimisation analysis; COA, cost-offset analysis; CUA, cost-utility analysis; DMD, Duchenne muscular dystrophy; EU, European Union; HCRU, healthcare resource use; N/A, not applicable; SLR, systematic literature review; UK, United Kingdom

Results

PRISMA flow diagram

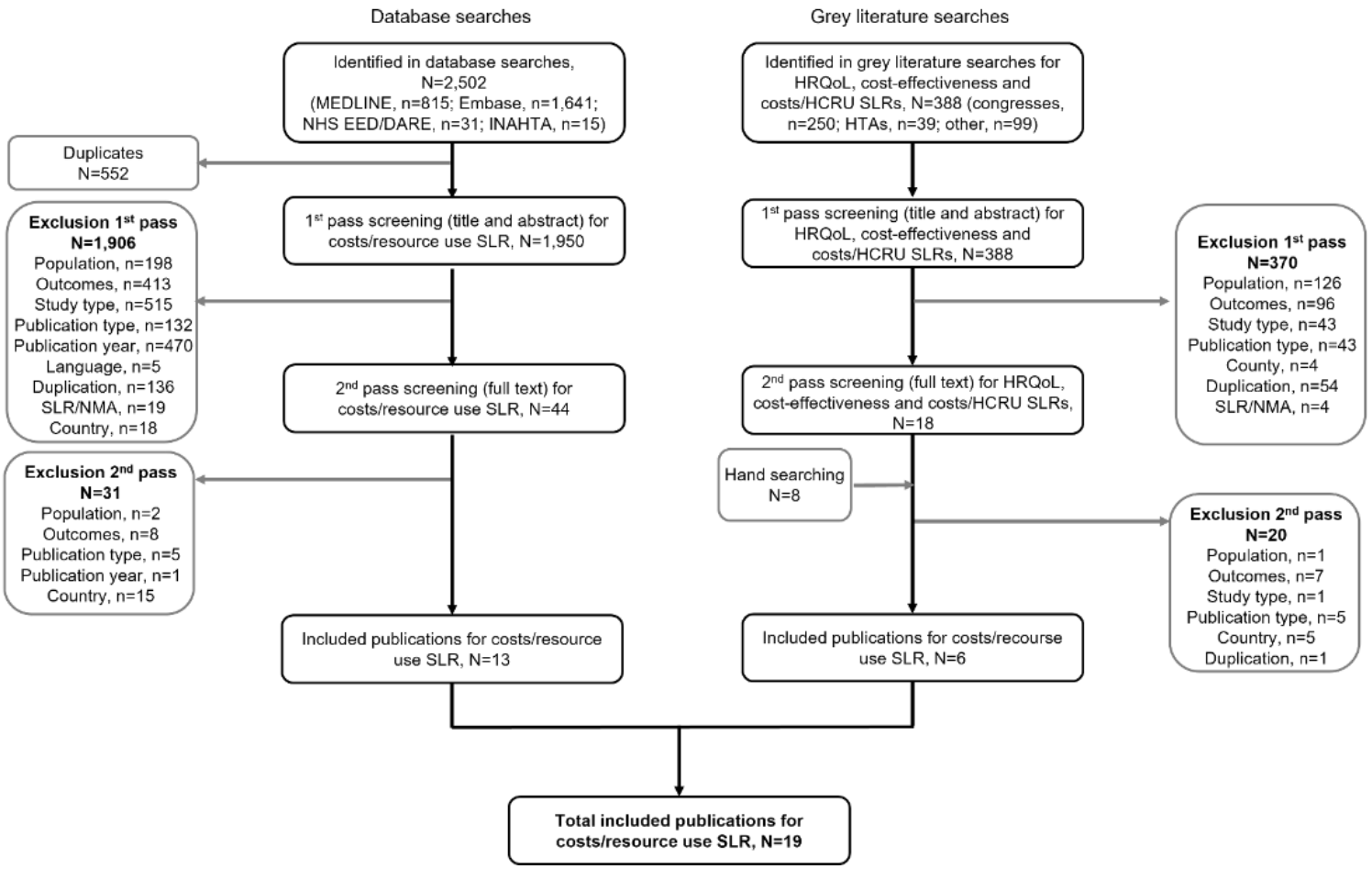
For the original SLR, of the 2,502 papers identified for the cost-effectiveness, HRQoL, and costs and resource use SLRs by the database searches, 552 were removed as duplicates, and the titles and abstracts of 1,950 papers were reviewed for the costs and resource use SLR at first-pass screening. After exclusion of 1,906 papers, the full texts of 44 publications were reviewed at second-pass screening, of which 31 were subsequently excluded. A total of 13 papers met the pre-defined inclusion criteria from the database searches and were included in the costs and resource use review.

Of the 388 publications identified by grey literature searching, 370 were excluded following first-pass screening. Additionally, eight publications were identified through hand searching. Of the 26 publications, that were reviewed as full-text articles, 20 were excluded and six met the selection criteria for inclusion in the costs and resource use SLR.

Therefore, a total of 19 publications were included in the costs and resource use SLR from the database searches, grey literature searches, and hand searching. The flow of studies through the reviews is reported in the PRISMA flow diagram in Figure 60.

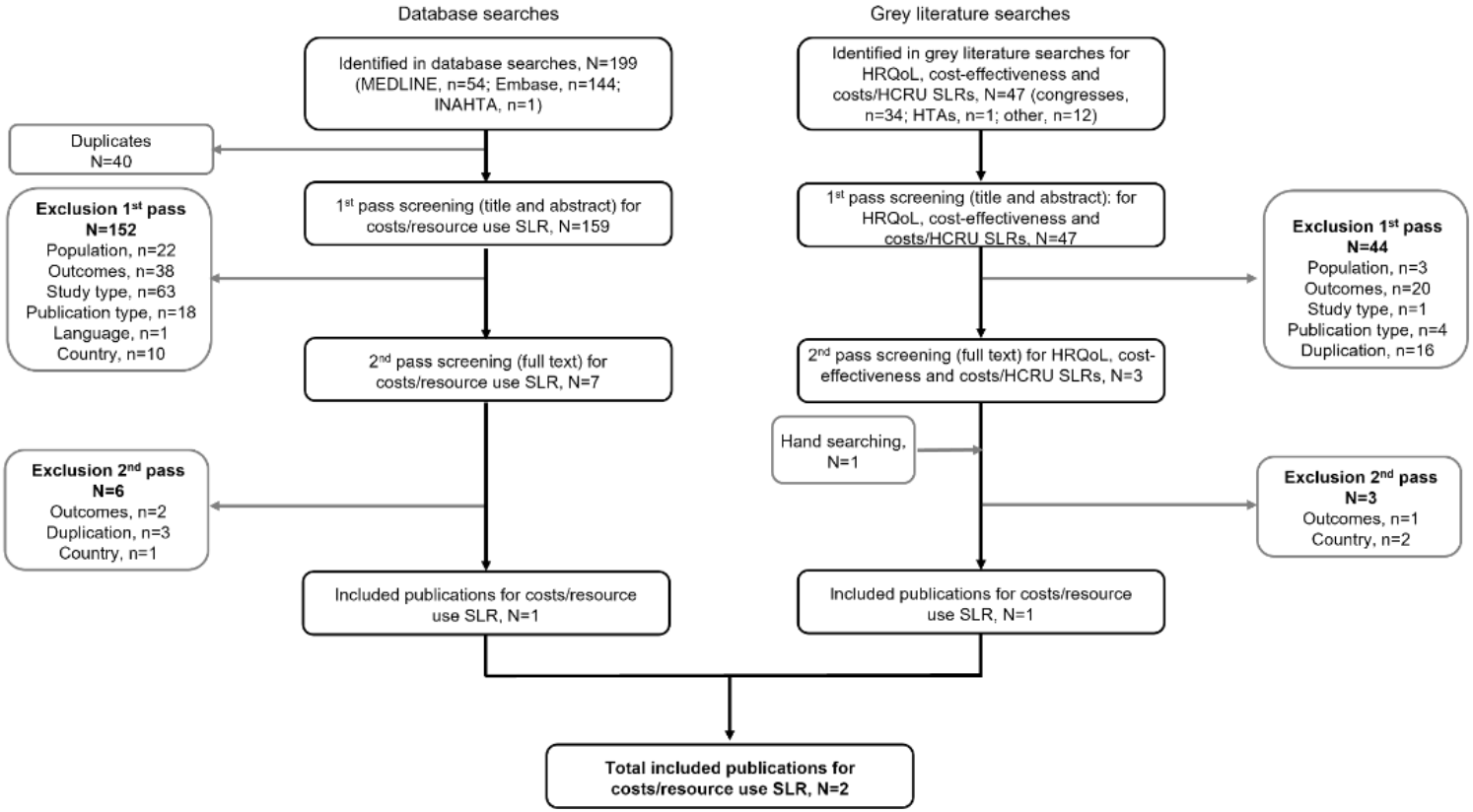
An update of the SLR was run, for the period 07 May 2024 to 07 November 2024, during which two new publications were found to be relevant to the SLR. The flow of studies through the reviews is reported in the PRISMA flow diagram in Appendix I.

Figure 60: PRISMA flow diagram for the original costs and resource use SLR


Database searches
Grey literature searches
Identified in database searches, N=2,502 (MEDLINE, n=815; Embase, n=1,641; NHS EED/DARE, n=31; INAHTA, n=15)
Identified in grey literature searches for HRQoL, cost-effectiveness and costs/HCRU SLRs, N=388 (congresses, n=250; HTAs, n=39; other, n=99)
Duplicates N=552
1st pass screening (title and abstract) for costs/resource use SLR, N=1,950
1st pass screening (title and abstract) for HRQoL, cost-effectiveness and costs/HCRU SLRs, N=388
Exclusion 1st pass N=1,906
Population, n=198
Outcomes, n=413
Study type, n=515
Publication type, n=132
Publication year, n=470
Language, n=5
Duplication, n=136
SLR/NMA, n=19
Country, n=18
Exclusion 1st pass N=370
Population, n=126
Outcomes, n=96
Study type, n=43
Publication type, n=43
County, n=4
Duplication, n=54
SLR/NMA, n=4
2nd pass screening (full text) for costs/resource use SLR, N=44
2nd pass screening (full text) for HRQoL, cost-effectiveness and costs/HCRU SLRs, N=18
Hand searching N=8
Exclusion 2nd pass N=31
Population, n=2
Outcomes, n=8
Publication type, n=5
Publication year, n=1
Country, n=15
Exclusion 2nd pass N=20
Population, n=1
Outcomes, n=7
Study type, n=1
Publication type, n=5
Country, n=5
Duplication, n=1
Included publications for costs/resource use SLR, N=13
Included publications for costs/recourse use SLR, N=6
Total included publications for costs/resource use SLR, N=19

Abbreviations: DARE, Database of Abstracts of Reviews of Effects; HCRU, healthcare resource use; HRQoL, health-related quality of life; HTA, health technology assessment; INAHTA; International Health Technology Assessment Database; NHS EED, National Institute for Health Research Economic Evaluation Database; NMA, network meta-analysis; PRISMA, preferred reporting items for systematic reviews and meta-analyses; SLR, systematic literature review

Figure 61: PRISMA flow diagram for the costs and resource use SLR update



Abbreviations: HCRU, healthcare resource use; HRQoL, health-related quality of life; HTA, health technology assessment; INAHTA; International Health Technology Assessment Database; PRISMA, preferred reporting items for systematic reviews and meta-analyses; SLR, systematic literature review

Complete reference lists for included and excluded publications

Included studies

As per eligibility criteria, 21 relevant publications were identified. The full list of the identified publications is presented in Table 114.

Table 114: List of studies included in the costs and resource use SLR

Author(s)	Year	Title
J. H. Rudolfsen; J. Vissing; U. Werlauff; et al.	2023	EE196 Real World Evidence on the Burden of Disease for Patients and Their Nearest Relatives–the Case of Duchenne muscular dystrophy
C. Khanji	2023	EE489 The Economic Burden of Caring for a Child with Duchene Muscular Dystrophy in Canada: A Caregiver Survey
D. Castro; J. Evans; C. Jones; et al.	2023	Introduction to the Duchenne muscular dystrophy Burden-of-Illness Study Expanded (US AND SPAIN)
G. Volfova; K. Podolska; J. Berezna; et al.	2023	PCR233 Socioeconomic Impact of Muscular Dystrophies on Patients and Their Caregivers in the Czech Republic
J. Strober; K. Ishigaki; V. Merla; et al.	2023	RWD130 Healthcare Resource Utilization for Pediatric and Adolescent Duchenne muscular dystrophy Patients: Analysis of Real-World Data
NICE HST22	2023	Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene
Lenka Jurikova, Karolina Podolska, Barbora Decker, et al.	2023	Duchenne muscular dystrophy–medical, psychological and financial aspects of the disease. Results of the survey
Kyttälä M, Auranen M, Vesikansa A, et al.	2023	A Nationwide Feasibility Study and Study Concept to Assess the Burden of Duchenne muscular dystrophy (DMD) in Finland
P. Labisa; V. Andreozzi; M. Mota; et al.	2022	Cost of Illness in Patients with Duchenne muscular dystrophy in Portugal: The COIDUCH Study
G. Chen; B. Sharif; B. Gerber; et al.	2022	EPH153 A Population-Based Study of the Epidemiology, Healthcare Resource Utilization and Costs of Duchenne muscular dystrophy in Alberta, Canada
SMC2327	2021	ataluren (Translarna)
D. Flores; M. P. Ribate; M. Montolio; et al.	2020	Quantifying the economic impact of caregiving for Duchenne muscular dystrophy (DMD) in Spain
D. Hind; J. Parkin; V. Whitworth; et al.	2017	Aquatic therapy for boys with Duchenne muscular dystrophy (DMD): an external pilot randomised controlled trial

E. Landfeldt; L. Alfredsson; V. Straub; et al.	2017	Economic Evaluation in Duchenne muscular dystrophy: Model Frameworks for Cost-Effectiveness Analysis
L. J. Teoh; E. A. Geelhoed; K. Bayley; et al.	2016	Health care utilization and costs for children and adults with Duchenne muscular dystrophy
E. Landfeldt; P. Lindgren; C. F. Bell; et al.	2016	Quantifying the burden of caregiving in Duchenne muscular dystrophy
M. Cavazza; Y. Kodra; P. Armeni; et al.	2016	Social/economic costs and health-related quality of life in patients with Duchenne muscular dystrophy in Europe
E. Landfeldt; A. Mayhew; M. Eagle; et al.	2015	Development and psychometric analysis of the Duchenne muscular dystrophy Functional Ability Self-Assessment Tool (DMDSAT)
O. Schreiber-Katz; C. Klug; S.Thiele; et al.	2014	Comparative cost of illness analysis and assessment of health care burden of Duchenne and Becker muscular dystrophies in Germany
Update review (November 2024)		
L. De Waele; J. Cremers; E. Debien; et al.	2024	Quantifying the burden-of-illness of Duchenne muscular dystrophy in Belgium: an interim analysis of a site-based survey
C. Llewellyn Morgan; J. Godfrey; F Chandler; et al.	2024	Epidemiology and healthcare resource utilisation associated with Duchenne muscular dystrophy

Abbreviations: DMD, Duchenne muscular dystrophy; DMDSAT, Duchenne muscular dystrophy Functional Ability Self-Assessment Tool; HST, highly specialised technology; NICE, National Institute for Health and Care Excellence; SMC, Scottish Medicines Consortium; US, United States.

Excluded studies

Overall, 2,327 papers were excluded during first- and second-pass screening in the original costs and HCRU SLR. Through database searches, 1,906 papers were excluded during first-pass screening and 31 were excluded during full-text screening. Through grey literature searches, 370 publications were excluded during first-pass screening and 20 were excluded during full-text screening.

For the SLR update, a total of 205 publications were excluded; for the database searches 152 were excluded during first-pass screening and six during second-pass screening and for the grey literature searches 44 were excluded during first-pass screening and three during second-pass screening.

Due to the large number of studies excluded, these are attached as separate files (Italfarmaco 2024o, Italfarmaco 2024p, Italfarmaco 2024q, Italfarmaco 2024r, Italfarmaco 2024m, Italfarmaco 2024n).

Outcomes of included publications

Table 115 presents the study characteristics for the 21 identified publications.

Table 115: Summary of results of the included costs and HCRU studies

Author/year Currency, cost year Source publication	HCRU (data or reference used in study)	Direct medical costs	Direct non-medical costs	Indirect costs	Total costs	AE costs/ long-term impact of steroid costs/ co-morbidity costs
Rudolfsen, 2023 EURO	Ventilation and assistive devices: 73% of the patients were found to have respiratory failure and 67% were dependent on assistive devices such as respirator or wheelchair Mean age at first respiratory therapy was 15.3 years (141/213 patients), and 23.2 years for in-home mechanical ventilation (127/213 patients) Surgery: Most frequent surgery for DMD patients were scoliosis (38%) or Achilles tendon	Healthcare costs of DMD patients compared to controls increased with age: Inpatient care (€) patients vs. controls 0–7yr: 1,076 vs. 352 8–11yr: 1,833 vs. 144 12–17yr: 9,557 vs. 238 18+yr: 12,656 vs. 446 Prescription medicine (€) patients vs. controls 0–7yr: 143 vs. 41 8–11yr: 382 vs. 74 12–17yr: 416 vs. 143	NR	Labour market: Productivity loss was 20,200 annually for DMD patients Education: Both DMD patients and siblings had lower school grades and required more special education than controls. For patients, the costs of this was 180,900 (11 years school period) Labour market: Productivity loss no difference were found for parents and siblings Labour market: Productivity loss no difference were found	Total attributable costs due to DMD: At 20 years post-diagnosis: 1,524,000 At 30 years: 2,365,800	NR

	surgery (29%) Hospital contacts were significantly higher for DMD patients two years before/after diagnosis versus controls leading to 60 extra hospital admissions and 200 extra outpatient visits 20 years post-diagnosis	18+yr: 414 vs. 109 Outpatient care (€) patients vs. controls 0–7yr: 892 vs. 173 8–11yr: 1,510 vs. 131 12–17yr: 2,027 vs. 198 18+yr: 1,786 vs. 324 Primary care (€) patients vs. controls 0–7yr: 474 vs. 182 8–11yr: 781 vs. 93 12–17yr: 851 vs. 90 18+yr: 842 vs. 151		for parents and siblings Education: Both DMD patients and siblings had lower school grades and required more special education than controls		
Khanji, 2023 Canadian dollars, 2022	NR	Medical equipment: 1% Mental health: 1%	The median annual out-of-pocket costs related to DMD was $22,106.52 (11,267.77; 34,897.83) with 89% of these expenses that were due to car and home	Median (IQR) annual income was $40,000 ($40,000) prior to diagnosis. It dropped to $10,000 ($0) within 3 years of the diagnosis and increased to $105,000 ($5,000) 4 to	NR	NR

adaptations. Median (IQR) annual out-of-pocket costs related to DMD were $23,446 ($22,312) with 91% of these expenses due to home and car adaptations and payments. Out-of-pocket costs associated with home adaptation, home payments, and car adaptation differed the greatest between ambulatory and non-ambulatory health states. Home adaptation: 51% Home payments: 22% Car payments: 14%	7 years after diagnosis. Seven caregivers (35%) became unemployed following the DMD diagnosis. Five caregivers (63%) reported they lost or refused a promotion (valued between $1,000 and $20,000) due to their caregiving responsibilities. Nine caregivers were employed at the time of survey completion. Days worked per week: Prior to DMD diagnosis, 9 (100%) worked 5 days; at survey completion, 2 (22%) worked 4 days and 7 (78%) worked 5 days Hours worked per week: Prior to DMD diagnosis, 1

			Fuel and transportation: 3% Financial health: 1% Other costs: 3%	(11%) worked 25-32 hrs, 5 (56%) worked 33-40 hrs, 3 (33%) worked >40 hrs; at survey completion, 1 (11%) worked <8 hrs, 1 (11%) worked 25-32 hrs, 6 (67%) worked 33-40 hrs, 1 (11%) worked >40 hrs		
Castro, 2023 Currency/cost year NR	Mean HCRU in the last 12 months by DS Mean (SD) scheduled physician consultations DS1: 2.50 (1.97) DS2: 3.45 (2.78) DS3: 3.70 (1.52) DS4: 3.03 (2.10) DS5: 4.93 (3.36) DS6: 4.39 (3.13) DS7: 4.72 (3.94)	NR	NR	NR	NR	NR

DS8: 5.00 (3.04)

Mean (SD) scheduled nurse specialist consultations

DS1: 1.35 (1.23)

DS2: 1.48 (1.78)

DS3: 2.53 (2.70)

DS4: 1.59 (1.72)

DS5: 3.29 (3.15)

DS6: 2.44 (1.89)

DS7: 3.28 (5.11)

DS8: 4.00 (3.43)

Mean (SD) hospitalisations

DS1: 0.21 (0.59)

DS2: 0.57 (1.13)

DS3: 0.58 (0.68)

DS4: 0.47 (0.72)

DS5: 0.93 (0.92)

DS6: 1.06 (1.00)

DS7: 1.22 (1.44)

DS8: 1.78 (1.92)

Mean (SD) surgeries

DS1: 0.03 (0.17)

DS2: 0.05 (0.22)

DS3: 0.28 (0.60)

DS4: 0.16 (0.37)

DS5: 0.57 (0.65)

DS6: 0.33 (0.49)

DS7: 0.22 (0.55)

DS8: 0.56 (0.73)

Mean (SD) tests

DS1: 4.06 (3.55)

DS2: 2.74 (3.97)

DS3: 4.98 (6.15)

DS4: 3.84 (4.48)

DS5: 5.14 (5.16)

DS6: 7.00 (8.00)

DS7: 5.28 (4.76)

	DS8: 6.11 (5.23) Mean (SD) treatments DS1: 1.97 (1.85) DS2: 2.24 (2.21) DS3: 2.6 (1.93) DS4: 3.06 (2.34) DS5: 3.57 (1.87) DS6: 2.89 (2.27) DS7: 3.61 (2.00) DS8: 3.00 (1.66)					
Volfova, 2023 EURO	Significant time burden for caregivers: Average ~ four hours spent daily assisting with disease-related activities. Additionally, caregivers spent an average of 29 hours per month in health facilities or traveling to them.	Out-of-pocket costs: (EURO) Traveling to health facilities: 1,320/year Medical devices: 852 Caregivers: Up to 71% regular pay for nutritional supplements: average 84 EURO / month	Care allowance: Average at 6yrs age Number of times applied: Average >twice Reassessment of level of dependence: 79% Appeal in relation to illness: 51 (64%) Other benefits:	Only 31 caregivers (39%) had regular assistance from another caregiver. Caregivers pay: Transport for medical examination: Average 109 EUR/month (79% respondents do not ask for reimbursement from health insurance company)	NR	NR

Mean number of specialists seen excluding GPs: 4.3.

Mean time spent per month in healthcare facilities: 11 hours. % patients with DMD who have taken or are taking corticosteroids: 84%. Nutritional supplements: 64% patients take

Mobility allowance: 81% of respondents

Total allowances:

33 respondents receive a regular monthly allowance from a foundation in connection with their illness, on average 284 EURO per month

Social services: Yes: 25%. Of these:

Personal assistance: 38%

Social counselling: 29%

Respite care: 17%

Social rehabilitation: 13%

Day care: 4%

Education:

Of 55 DMD patients who go to school, 84% have a teaching assistant–in 93% provided by school.

Of the respondents, 29% said school made special accommodations because of the patient.

Care/work:

40 respondents (50%): no substitute caregiver.

Of those who had: 33 (45%) responded that the substitute is the other parent

Employment:

Part-time: 22%

Unemployed: 21%

Full-time: 20%

Self-employed: 11%

				Other: caring for a loved one: 11% Maternity or parental leave: 8% Work contract (<300hrs/year): 4% Work contract (<20 hrs/week): 4% 89% of those unemployed state caring for the disabled patient is the reason (general population = <3%). In total, 94% of carers responded that their educational attainment was not affected by a neuromuscular disease in the family.	
Strober, 2023	Mean (SD) number of hospitalisations in the last 12 months due to DMD: All patients: 0.2 (0.54) 0–12 years: 0.2 (0.50)	NR	NR	NR	NR	NR

13–18 years: 0.2 (0.59)

Number (%) of patients hospitalised due to DMD in the last 12 months:

All patients: 63 (14.8%)

0–12 years: 34 (12.9%)

13–18 years: 29 (18.0%)

Number (%) of hospitalisations involving ICU stay in the last 12 months:

All patients: 9/63 (14.3)

0–12 years: 3/34 (8.8%)

13–18 years: 6/29 (20.7%)

Number (%) of patients who had surgery for DMD-related issue in the last 12 months:

All patients: 11/63 (17.5%)

0–12 years: 2/34 (5.9%)

13–18 years: 9/29 (31.0%)

Number of physicians seen in the last 12 months:

All patients: 4.0

0–12 years: 3.7

13–18 years: 4.5

Number of consultations with healthcare professionals in the last 12 months:

All patients: 21.3

0–12 years: 16.9

13–18 years: 28.5

Number of tests conducted to monitor condition in the last 12 months:

All patients: 11.3

0–12 years: 9.7

13–18 years: 13.7

Proportion of patients using mobility aids/supports:

Any aid/support: 61.2% of children and 84.5% of adolescents

Orthoses: 32.2% of children and 42.4% of adolescents

Electric wheelchair: 9.8% of children and 46.6% of adolescents

Manual wheelchair: 12.9% of children and 16.8% of adolescents

Stroller/pram: 14.4% of children

Electric scooter: 1.9% of children and 5.0% of adolescents

Proportion of patients with home modifications:

All patients (n=359): 63.5%

0–12 years (n=228): 52.2%

13–18 years (n=131): 83.2%

				Physician-reported home modifications (n=119 children and n=109 adolescents): Adapted bathroom: 47.9% of children and 62.4% of adolescents Adapted bedroom: 36.1% of children and 51.4% of adolescents Fitted grab bars/railings: 37.8% of children and 44.0% of adolescents Installation of ramps: 20.2% of children and 29.4% of adolescents Fitted a stair lift: 16.8% of children and 22.9% of adolescents		
HST22, NICE GBP, 2022	NR	NR	NR	The price for ataluren is £2,532 per box of thirty 125-mg sachets, £5,064 per box of thirty 250-mg sachets and £20,256 per	NR	NR

				box of thirty 1,000-mg sachets		
Jurikova, 2023 EURO	NR	Monthly €54 on vitamins or other dietary supplements Monthly €21 on medication	Monthly €42 on medical devices	Monthly €41 on travel costs	Average 20% of family's income	NR
Kyttälä, 2023	Average per year in total, n: Primary care contacts, 55.8 Primary care visits, 47.5 Primary care contacts other than visits, 8.3 Secondary care contacts, 967.7 Secondary care visits, 838.7 Secondary care inpatient periods, 129.0 Average per year per patient, n Primary care contacts, 0.5	NR	NR	NR	NR	NR

Primary care visits, 0.4

Primary care contacts other than visits, 0.1

Secondary care contacts, 8.1

Secondary care visits, 7.0

Secondary care inpatient periods, 1.1

2011 (n=121)

Per year in total, n:

Primary care contacts, 37

Primary care visits, 29

Primary care contacts other than visits, 8

Secondary care contacts, 679

Secondary care visits, 504

Secondary care inpatient periods, 175

Per year per patient, n

Primary care contacts, 0.3

Primary care visits, 0.2

Primary care contacts other than visits, 0.1

Secondary care contacts, 5.6

Secondary care visits, 4.2

Secondary care inpatient periods, 1.4

2012 (n=123)

Per year in total, n:

Primary care contacts, 40

Primary care visits, 37

Primary care contacts other than visits, 3

Secondary care contacts, 626

Secondary care visits, 473

Secondary care inpatient periods, 153

Per year per patient, n

Primary care contacts, 0.3

Primary care visits, 0.3

Primary care contacts other than visits, 0.0

Secondary care contacts, 5.1

Secondary care visits, 3.8

Secondary care inpatient periods, 1.2

2013 (n=117)

Per year in total, n:

Primary care contacts, 58

Primary care visits, 53

Primary care contacts other than visits, 5

Secondary care contacts, 772

Secondary care visits, 640

Secondary care inpatient periods, 132

Per year per patient, n

Primary care contacts, 0.5

Primary care visits, 0.5

Primary care contacts other than visits, 0.0

Secondary care contacts, 6.6

Secondary care visits, 5.5

Secondary care inpatient periods, 1.1

2014 (n=120)

Per year in total, n:

Primary care contacts, 51

Primary care visits, 41

Primary care contacts other than visits, 10

Secondary care contacts, 865

Secondary care visits, 722

Secondary care inpatient periods, 143

Per year per patient, n

Primary care contacts, 0.4

Primary care visits, 0.3

Primary care contacts other than visits, 0.1

Secondary care contacts, 7.2

Secondary care visits, 6.0

Secondary care inpatient periods, 1.2

2015 (n=121)

Per year in total, n:

Primary care contacts, 35

Primary care visits, 35

Primary care contacts other than visits, 0

Secondary care contacts, 958

Secondary care visits, 822

Secondary care

inpatient periods, 136

Per year per patient, n

Primary care contacts, 0.3

Primary care visits, 0.3

Primary care contacts other than visits, 0.0

Secondary care contacts, 7.9

Secondary care visits, 6.8

Secondary care inpatient periods, 1.1

2016 (n=121)

Per year in total, n:

Primary care contacts, 20

Primary care visits, 18

Primary care contacts other than visits, 2

Secondary care contacts, 1012

Secondary care visits, 871

Secondary care inpatient periods, 141

Per year per patient, n

Primary care contacts, 0.2

Primary care visits, 0.1

Primary care contacts other than visits, 0.0

Secondary care contacts, 8.4

Secondary care visits, 7.2

Secondary care inpatient periods, 1.2

2017 (n=122)

Per year in total, n:

Primary care contacts, 63

Primary care visits, 59

Primary care contacts other than visits, 4

Secondary care contacts, 1076

Secondary care visits, 939

Secondary care inpatient periods, 137

Per year per patient, n

Primary care contacts, 0.5

Primary care visits, 0.5

Primary care contacts other than visits, 0.0

Secondary care contacts, 8.8

Secondary care visits, 7.7

Secondary care inpatient periods, 1.1

2018 (n=121)

Per year in total, n:

Primary care contacts, 121

Primary care visits, 105

Primary care contacts other than visits, 16

Secondary care

contacts, 1121

Secondary care visits, 1000

Secondary care inpatient periods, 121

Per year per patient, n

Primary care contacts, 1.0

Primary care visits, 0.9

Primary care contacts other than visits, 0.1

Secondary care contacts, 9.4

Secondary care visits, 8.4

Secondary care inpatient periods, 1.0

2019 (n=119)

Per year in total, n:

Primary care contacts, 77

Primary care visits, 61

Primary care contacts

other than visits, 16

Secondary care contacts, 1222

Secondary care visits, 1134

Secondary care inpatient periods, 88

Per year per patient, n

Primary care contacts, 0.6

Primary care visits, 0.5

Primary care contacts other than visits, 0.1

Secondary care contacts, 10.3

Secondary care visits, 9.5

Secondary care inpatient periods, 0.7

2020 (n=120)

Per year in total, n:

Primary care contacts, 56

	Primary care visits, 37 Primary care contacts other than visits, 19 Secondary care contacts, 1346 Secondary care visits, 1282 Secondary care inpatient periods, 64 Per year per patient, n Primary care contacts, 0.5 Primary care visits, 0.3 Primary care contacts other than visits, 0.2 Secondary care contacts, 11.2 Secondary care visits, 10.7 Secondary care inpatient periods, 0.5					
Labisa, 2022 EURO, 2019	Unit costs for both medical and non-medical goods and services	Two times higher in the non-ambulant stage than in the	Mean costs during the non-ambulant stage were over twice	Indirect costs of primary caregivers from loss of productivity	Mean (SD) per patient total	NR

were obtained, preferably from caregivers and/or patients or alternatively from national databases, legislation, and wholesalers Informal care costs were valued according to the proxy good method (time spent on informal care is valued according to the price of a close market substitute) Indirect costs due to absenteeism and changes in working situation or presenteeism of the primary caregiver were estimated using the human capital approach (average gross wage of the individual is considered a good proxy for the loss	ambulant stage. Third highest contributor to total costs Mean (SD) per patient annual costs, % total Ambulant: 3,708 (1,561), 19% Hospital care: 25 (70), <1% Physician/other HCP: 3,126 (1,195), 16% Tests and diagnostics: 69 (61), <1% Drug treatments *: 175 (150), <1% Nutrition support & other health products: 7 (21), <1% Medical devices: 305 (403), 2% Non-ambulant: 9,063	those of the ambulant stage. Main contributor to total costs Mean (SD) per patient annual costs, % total Ambulant: 11,890 (5,547), 60% House and/or care adaptations: NR Non-medical services: 1,894 (3,298), 10% Informal care: 9,996 (3,711), 50% Non-ambulant: 29,717 (14,374), 61% House and/or care adaptations: 7,329 (15,257), 15% Non-medical services:	due to DMD were more than three times higher for the non-ambulant group than for the ambulant group Mean (SD) per patient annual costs, % total Ambulant: 4,395 (6,415), 22% Absenteeism and/or changes in work: 2,824 (4,978), 14% Presenteeism: 1,572 (3,506), 8% Non-ambulant: 10,211 (6,352), 21% Absenteeism and/or changes in work: 9,292 (6,947), 19% Presenteeism: 919 (1,963), 2% CAREGIVER EMPLOYMENT STATUS, n (%) ambulatory vs. non-ambulatory:	annual cost: Ambulant: 19,993 (5,944) Non-ambulant: 48,991 (15,394) Estimated decreasing effect of age independent of patients' DS Annualised lifetime costs started at 25,000 and slightly declined as age increased for ambulant patients (age range 2–10 years) Although non-ambulant patients also presented a decreasing annualised lifetime cost, the model fitted suggested a greater

	of labour productivity). Each hour of lost productivity was valued according to the Portuguese average gross wage assuming the national average working hours in 2017 (adjusted for sex)	(5,416), 19% Hospital care: 889 (1,241), 2% Physician/other HCP: 3,157 (2,486), 6% Tests and diagnostics: 214 (292), <1% Drug treatments *: 333 (362), <1% Nutrition support/other health products: 889 (2,889), 2% Medical devices: 3,582 (2,497), 7% *excludes ataluren and a staminal treatment	1,615 (2,226), 3% Informal care: 20,772 (9,081), 42%	Not working: 3 (38%) vs. 28 (74) Altered due to DMD: 2 (25%) vs. 26 (68%) Stopped working: 1 (13%) vs. 22 (58%) Reduced hours: 1 (13%) vs. 4 (11%) Hours dedicated to informal care: Mean 6.1 (SD 2.0) vs. mean 14.0 (SD 5.1)	disease burden around the mean age of LOA followed by a slightly linear decrease until around 20 years age, when the cost stabilized at around 50,000 per year
Chen, 2022 Canadian dollars	All-cause HCRU in the first-year post-diagnosis included a mean (SD): Hospitalisations: 0.88 (1.73) Number of days hospitalised:	Mean (SD) all-cause direct costs in 1st year post-diagnosis: $27,969.77 ($36,183.26)	NR	NR	NR

	16.88 days (49.19) GP visits: 6.04 (5.92) Specialist visits: 57.88 (106.11) Ambulatory care visits: 27.08 (18.70)					
SMC2327 GBP, 2021	Landfeldt et al. 2017	NR	NR	Ataluren cost per cycle at list price (assuming average weight of 35kg): £84,774 Cost per year: £123,224 to £739,344	NR	NR
Flores, 2020 EURO	NR	All families apart from one (97.2% n = 36) incurred in monthly medical costs. 52.8% of them (n = 35) spent less than 50 €/month, 33.3% (n = 35) between 50 and 100 €/month, and 11.1% (n = 35) more than 100 €/month.	In relation with expenditure in formal care, 11 families (30.5% n = 36) incurred in such costs with seven of them (19.4% n = 36) spending less than 250 €/month, three (8.3% n = 36) between 250 and 500 €/month, and one	In terms of employment impact, 29 (80.5%) households declared to have suffered work changes being the mothers the ones making adjustments in 25 cases, and the fathers in 21 cases. Timetable adjustments are the most common change for both mothers (14	NR	NR

		(2.7%) more than 500 €/month with an average of 88.06 € per family and month (SD 189.2).	cases, 38.9%) and fathers (13 cases, 36.1%). During the previous month to the survey, the average caregiver had to take 8.83 h (SD = 13.7) (range 0–76) from work to take care for the DMD patient. Approximately 22.2% of households reported that someone in the family had to quit working to care for their child, and 17% had to change job.		
Hind, 2017 GBP Intervention costs to families and the NHS were estimated using information from the quantitative and qualitative components of the study	NR	Over 6 months, the estimated direct NHS costs ranged from £1970 to £2734	Over 6 months, the estimated societal costs ranged from £2541 to £3775	NR	NR

Landfeldt, 2017 GBP, 2015 British National Formulary (BNF); 2012. Department of Health. National schedule of reference costs 2010–11 for NHS trusts. Personal Social Services Research Unit (PSSRU). Unit costs of health & social care 2011. Drummond M. Oxford: Oxford University Press; 2005. Kobelt G. London: Office of Health Economics; 2002.	Direct medical and non-medical costs of DMD were calculated using data on resource use and national reference prices Costs for medical aids and devices were obtained through input from experts within the Translational Research in Europe – Assessment and Treatment of Neuromuscular Diseases (TREAT-NMD) network Indirect costs of DMD were quantified in accordance with the human capital approach, in which the societal loss in production is valued at the cost of employment (i.e. the national mean gross income plus	Mean (SD) Model I: initial score, 8340 (830); per lost score (multiplier), 1.057 (1.005) Model II: EA, 10,670 (140); LA, 11,190 (100); ENA, 16,490 (290); LNA, 27,590 (340) Model III: none, 11,520 (60); night-time, 31,710 (590); day- and night-time, 36,390 (840)	Mean (SD) Model I: initial score, 9120 (860); per lost score (multiplier), 1.04 (1.006) Model II: EA, 9740 (50); LA, 11,420 (50); ENA, 17,860 (110); LNA, 16,810 (90) Model III: none, 12,660 (60); night-time, 14,610 (240); day- and night-time, 15,500 (190)	Mean (SD) Patient: Model I: initial score, 14,230 (1540) Model II: EA, 0; LA, 0; ENA, 0; LNA, 14.230 (1540) Model III: none, 14,230 (1540); night-time, 14,230 (1540); day- and night-time, 14,230 (1540) Caregiver Model I: initial score, 6360 (740); Per lost score (multiplier), 1.037 (1.006) Model II: EA, 7180 (190); LA, 8340 (150); ENA, 12,810 (370); LNA, 11,240 (260) Model III: none, 9160 (120); night-time, 10,490 (420); day- and night-time, 12,860 (640)	Mean (SD) Model I: initial score, 23,870 (1580); per lost score (multiplier), 1.053 (1.003) Model II: EA, 27,590 (350); LA, 30,950 (260); ENA, 47,160 (710); LNA, 66,720 (1600) Model III: none, 34,520 (440); night-time, 61,490 (2600); day- and night-time, 83,250 (2210)	NR

	employer's costs and social fees)					
Teoh, 2016 Australian dollars, 2014 Medicare Benefits Schedule Book, National Hospital Cost Data Collection, Department of veterans' Affairs Allied Health schedules, and Pharmaceutical Benefits Scheme (Version 4.0; 2009). Access Economics. The cost of muscular dystrophy. Canberra: Access Economics; October 19, 2007.) Australian Bureau of Statistics. Average Weekly Earnings, Australia.	Annual levels of healthcare utilisation for individuals with DMD, %, mean (median) Primary care practitioners: GP: 92%, 5.0 (4) Practice nurse: 22%, 0.7 (0) Health visitor: 13%, 1.7 (0) Specialist physicians: 94% Neurologist: 73%, 1.6 (2) Paediatrician: 38%, 1.0 (0) Orthopaedic specialist: 20%, 0.4 (0) Cardiologist: 71%, 1.2 (1) Respiratory physician: 64%, 1.3 (1) Geneticist: 9%, 0.1 (0)	Annual per person costs of care for individuals with DMD: Mean all: $10,046 Median all: $4,509 The highest health costs were driven largely by overnight hospital admissions related to a few major surgical procedures, respiratory conditions, and cardiac complications. These admissions contributed to 78% of the total hospital cost in this population Annual levels of cost for individuals with DMD, mean (median) Primary care practitioners: $464 ($287)	Annual per person costs of care for individuals with DMD: Mean all: $33,557 Median all: 23,872	Annual per person costs of care for individuals with DMD: Mean all: $3,008 Median all: $582 Working parents reported a mean loss of 11.7 working days in the last 12 months, (median: 4 days). These productivity losses translate to an average of $3,066 per working parent per year. Our results also showed a higher proportion (57%) of parents who report reduced working hours due to the caregiving demands of their child, and an additional 5% who reported moving to a lower paying	Annual per person costs of care for individuals with DMD: Mean all: $46,669 Median all: $32,799 Total direct costs, comprised of non-medical and healthcare costs were responsible for the vast majority of annual costs, contributing 72% and 22%, respectively. Productivity losses only contributed 6% of the total annual cost.	Mean healthcare costs: On GCC: $8,137 Not on GCC: $13,810 Overall annual total costs lower on GCC vs. not: On GCC: $41,718 Not on GCC: $56,428 These differences between health and total annual costs did not reach statistical significance. Direct costs varied with level of wheelchair dependence, with significant differences in cost seen between those who "Never"

Canberra: Australian Bureau of Statistics; 2014)	Endocrinologist: 12%, 0.36 Allied Health Therapy: 93% Physiotherapist: 71%, 6.4 (2) Speech therapist: 28%, 1.9 (0) Occupational therapist: 64%, 3.5 (2) Hydrotherapy: 20%, 5.3 (0) Wheelchair clinic: 24%, 0.5 (0) Psychologist: 17%, 0.7 (0) Genetic counsellor: 5%, 0.1 (0) Orthotics: 12%, 0.24 Dietician: 14%, 0.38 Hospital visits (incl. ED): Any encounter: 43%, 1 (0) Day stay: 34%, 0.58 (0) Overnight admission	Specialist physicians: $617 ($513) Allied Health Therapy: $1,641 ($902) Hospital visits (incl. ED): $5,802 ($0) Prescription medication: $567 ($353) Diagnostic test: $476 ($136) Annual health cost by quartiles was $2,306, $4,509, $8,856, and $209,560. Costs at 90%, 95%, and 99% were 4 to 21 times higher than the median cost: $18,941, $23,648, and $96,846 Health costs were dominated by hospital care, which contributed to 57% of mean costs The majority (84%) of	job. Notably, 21% of parents reported stopping work entirely, and more than 29% reported reducing working hours due to their child's condition.	use a wheelchair and those completely wheelchair bound (p=0.001). Total costs (sum of direct and indirect costs) also differed with level of wheelchair use. The highest costs were observed in individuals who were entirely wheelchair dependent ($65,050), which were significantly different from the total cost of individuals with no wheelchair use (p=0.003). In terms of reported medical comorbidities, individuals with respiratory conditions had significantly higher total costs

	(days): 25%, 1.92 (0) Prescription medication: 85% Prednisolone: 46% Deflazacort: 19% ACE inhibitor/cardiac glycoside: 38% Diagnostic test: 53% Blood test: 43% Bone density scan: 25% ECG: 22% Sleep study: 19%	healthcare costs was attributable to 3 categories of health services; hospital admissions (including 7% due to day admissions, and 49% due to overnight admissions), allied health therapy (16%), and physician and specialist visits (11%).			(p=0.0028), which were on average $37,015 more than those without a reported respiratory condition. Individuals with "Other" reported comorbidities (most commonly reported were heart conditions and asthma) had over 3 times higher healthcare costs (p=0.1165) and 60% higher total costs than those without such comorbidities (p=0.0067)
Landfeldt, 2016	NR	Annual household cost burden (includes non-reimbursed payments for insurance premiums, co-payments for medical and community services and medications, and out-of-pocket payments for investments (e.g., non-reimbursed payments for medical and non-medical aids and devices and investments to and	NR	NR	NR

		reconstructions of the home): <$1000: n = 380 (49%) $1000–$5000: n = 170 (22%) >$5000: n = 220 (29%) Hours of leisure time devoted to informal care (per week): <25: 294 (38%) 25–50: 203 (26%) >50: 273 (35%) Current situation: Employed: 469 (61%) Unemployed: 257 (33%) Retired: 26 (3%) Student: 12 (2%) Sick leave (>3 months): 6 (1%)				
Cavazza, 2016 EURO, 2012	NR	Mean (SD) annual costs for all patients, adult patients, and children patients in the UK Drugs All: 123 (185) Adults: 73 (150) Children: 185 (215) Medical tests	Mean (SD) annual costs for all patients, adult patients, and children patients in the UK Professional carer All: 819 (3,477) Adults: 1,475 (4,664) Children: NR (NR)	NR	Mean (SD) annual costs for all patients, adult patients, and children patients in the UK Total direct costs All: 34,658 (36,393)	NR

All: 685 (770)

Adults: 517 (506)

Children: 895 (1,011)

Medical visits

All: 2,144 (2,819)

Adults: 1,410 (1,138)

Children: 3,061 (3,987)

Hospitalisations

All: 535 (1,893)

Adults: 120 (381)

Children: 1,054 (2,822)

Health material

All: 338 (240)

Adults: 347 (220)

Children: 327 (278)

Healthcare transport

All: 62 (206)

Adults: 109 (273)

Non-healthcare transport

All: 356 (1,317)

Adults: 7 (19)

Children: 791 (1,955)

Social services

All: 579 (1,997)

Adults: 874 (2,653)

Children: 211 (597)

Total direct non-healthcare formal costs

All: 1,754 (6,790)

Adults: 2,356 (7,334)

Children: 1,001 (2,552)

Main informal carer

All: 17,123 (20,873)

Adults: 15,598 (21,463)

Children: 19,030 (21,408)

Adults: 29,480 (35,220)

Children: 41,130 (39,185)

		Children: 4 (10) Total direct healthcare costs All: 3,887 (5,535) Adults: 2,577 (1,841) Children: 5,525 (8,032)	Other informal carers All: 11,893 (19,119) Adults: 8,949 (17,833) Children: 15,573 (21,237) Total direct non-healthcare informal costs All: 29,016 (39,992) Adults: 24,547 (39,296) Children: 34,603 (42,645) Total direct non-healthcare costs All: 30,771 (36,942) Adults: 26,903 (35,595) Children: 35,605 (40,461)			
Landfeldt, 2015 Dollars, 2012 Landfeldt E. Neurology	NR	'The total DMDSAT score ranged from 0 (low functional ability) to 23 (high	'The total DMDSAT score ranged from 0 (low functional ability) to 23 (high	'The total DMDSAT score ranged from 0 (low functional ability) to 23 (high	'The total DMDSAT score ranged from 0 (low functional ability)	NR

2014;83:529–36.	functional ability). Mean (SE) annual costs initial score (full functional ability): 12,320 (1,230) Mean (SE) annual costs per lost score (multiplier): 1.057 (1.005)	functional ability). Mean (SE) annual costs initial score (full functional ability): 13,460 (1,270) Mean (SE) annual costs per lost score (multiplier) : 1.040 (1.006)	functional ability). Mean (SE) annual patient costs initial score (full functional ability): 0 (0) Mean (SE) annual patient costs per lost score (multiplier): 21,010 (2,280) Mean (SE) annual caregiver costs initial score (full functional ability): 9,400 (1,090) Mean (SE) annual caregiver costs per lost score (multiplier): 1.037 (1.006)	to 23 (high functional ability). Mean (SE) annual costs initial score (full functional ability): 35,240 (2,330) Mean (SE) annual costs per lost DMDSAT score (multiplier): 1.053 (1.003) The mean change in per patient annual cost of illness associated with a one-point change in DMDSAT total scare was 5.3% (95% CI, 4.6% to 5.9%, p<0.001). Spearman's p between predicted and observed

					patient utility was estimated at 0.61 (p<0.001).	
Schreiber-Katz, 2014 EURO, 2013	NR	Mean annual costs (min–max) Outpatient medical costs, 457 (0-4,644) stage I, 279 (0-3,046) stage II, 393 (0-4,644) stage III, 701 (0-2,973) stage IV, 552 (0-4,356) stage IV 523 (0-2,495) Inpatient medical costs, 1,613 (0-131,454) stage I, 585 (0-18,736) stage II, 804 (0-20,188) stage III,- stage IV, 1,540 (0-35,525) stage V, 6,673 (0-131,454)	Mean annual costs (SD) Costs for the housing situation, 4,043 (0-238,800) stage I, 55 (0-1,536) stage II, 83 (0-2,280) stage III, 1,064 (0-6,900) stage IV, 5,860 (0-192,000) stage V, 17,112 (0-238,800) Costs for personal assistance for school and work attendance, 883 (0-28,800) stage I, - stage II, 931 (0-15,000) stage III, 1,980 (0-9,600)	Mean annual costs (SD) Indirect costs caused by patients, 21,463 (0-43,740) stage I, - stage II, 11,100 (11,100-11,100) stage III, - stage IV, 18,734 (0-43,740) stage V, 28,529 (881-43,740) Indirect costs caused by parents, 7,220 (0-324,000) stage I, 13,078 (0-324,000) stage II, 3,855 (0-24,000) stage III, 8,046 (0-18,000) stage IV, 7,044 (0-45,100)	Mean annual costs: 78,913 stage I: 28,944 stage II: 33,268 stage III: 48,950 stage IV: 98,601 stage V: 164,855	NR

Rehabilitation program costs (in-/outpatient), 1,130 (0-30,053)

clinical severity stage I, -

stage II, 427 (0-17,017)

stage III, 2,780 (0-15,290)

stage IV, 2,086 (0-30,053)

stage IV, 954 (0-15,290)

Drug treatment costs, 330 (0-5,530)

stage I, 172 (0-967)

stage II, 373 (0-3,837)

stage III, 344 (0-746)

stage IV, 319 (0-5,530)

stage V, 550 (0-5,122)

Costs of rehabilitation services (e.g. physiotherapy), 4,732 (0-31,974)

stage IV, 1,481 (0-28,800)

stage V, -

Travel expenses, 1,102 (0-17,376)

stage I, 358 (0-1,479)

stage II, 741 (0-5,434)

stage III, 1,814 (108-7,264)

stage IV, 1,714 (0-17,376)

stage V, 915 (0-3,950)

Advocate support costs, 27 (0-8,333)

stage I, 1 (0-33)

stage II, 118 (0-8,333)

stage III, 0 (0-89)

stage IV, 0 (0-1,623)

stage V, 0 (0-59)

Investments in house adaptations, 3,059 (0-93,636)

stage V, 4,378 (0-12,000)

Total indirect COI, 28,683

stage I, 13,078

stage II, 14,955

stage III, 8,046

stage IV, 25,778

stage V, 32,907

stage I, 2,693 (0-10,658)	stage I, 2,826 (0-66,667)
stage II, 4,042 (0-31,974)	stage II, 0 (0-30,507
stage III, 5,204 (0-18,097)	stage III, 2,239 (0-12,421)
stage IV, 5,817 (0-24,657)	stage IV, 8,499 (0-93,636)
stage V, 6,478 (0-26,839)	stage V, 0 (0-13,853)
Costs of medical aids, 10,209 (0-103,977)	Investments in automobile adaptations, 408 (0-16,697)
stage I, 488 (0-4,368)	stage I, 62 (0-2,833)
stage II, 1,584 (0-11,450)	stage II, 559 (0-11,605)
stage III, 2,474 (1,285-4,805)	stage III, 2,609 (0-12,028)
stage IV, 11,153 (0-82,673)	stage IV, 776 (0-16,697)
stage V, 51,019 (1,342-103,977)	stage V, 0 (0-6,941)
Costs of respiratory management, 875 (0-12,087)	Other expenditures (e.g. artificial nutrition, alternative therapies), 83 (0-12,000)
stage I, 3 (0-34)	stage I, 41 (0-1,536)

stage II, 6 (0-34)	stage II, 223 (0-12,000
stage III, 163 (0-1,791)	stage III, -
stage IV, 1,522 (0-12,087)	stage IV, 14 (0-735)
stage V, 2,771 (0-6,779)	stage V, 510 (0-6,720)
Total direct medical costs, 19,346	Informal care costs, 21,279 (0-223,380)
stage I, 4,220	stage I, 8,303 (0-77,563)
stage II, 7,629	stage II, 8,029 (0-62,050)
stage III, 11,666	stage III, 19,532 (3,103-43,435)
stage IV, 22,989	stage IV, 31,490 (0-223,380)
stage V, 68,968	stage V, 44,443 (0-158,848)
	Total direct non-medical costs, 30,884
	stage I, 11,646
	stage II, 10,684
	stage III, 29,238
	stage IV, 49,834

			stage V, 62,980			
De Waele, 2024	In the last 12 months, the mean (SD) number of consultations with all HCPs was 12.0 (12.3), with 16 patients (64%) having ≥1 hospitalisation, 3 patients (12%) having surgery, and 19 patients currently receiving corticosteroids (76%).	NR	NR	NR	NR	NR
Morgan, 2024 GBP	Primary care: 8.01 contacts per patient year for DMD vs 2.56 for controls; IRR, 3.19 (95% CI, 3.11 to 3.28), p<0.001 Inpatients: 0.96 contacts per patient year for DMD vs 0.10 for controls; IRR, 9.24 (95% CI, 8.19 to 10.46), p<0.001	Healthcare costs for DMD vs controls Primary care: £224 per patient year for DMD vs £64 for controls; cost ratio, 3.30 (95% CI, 2.79 to 3.90), p<0.001 Inpatients: £1,712 per patient year for DMD vs £153 for controls; cost ratio, 12.67 (95% CI, 6.29 to	NR	NR	NR	NR

		25.52), p<0.001
	Accident and emergency: 0.50 contacts per patient year for DMD vs 0.25 for controls; IRR, 1.65 (95% CI, 1.53 to 1.81), p<0.001	Accident and emergency: £71 per patient year for DMD vs £38 for controls; cost ratio, 1.96 (95% CI, 1.51 to 2.55), p<0.001
	Outpatient: 9.00 contacts per patient year for DMD vs 0.95 for controls; IRR, 11.44 (95% CI, 10.95 to 11.96), p<0.001	Outpatient: £1,321 per patient year for DMD vs £92 for controls; cost ratio, 12.79 (95% CI, 10.11 to 16.18), p<0.001
		Prescription costs: £899 per patient year for DMD vs £69 for controls; cost ratio, 7.52 (4.21 to 13.44), p<0.0001
		Total costs: £4,227 per patient year for DMD vs £416 for controls; cost ratio, 9.33 (95% CI, 6.75 to 12.91), p<0.0001
		Healthcare costs by

	disease stage		
	Primary care: £176 per patient year for ambulatory (n=387) vs £274 for non-ambulatory without ventilation (n=188) vs £429 for non-ambulatory with ventilation (n=64)		
	Prescriptions: £460 per patient year for ambulatory vs £1,139 for non-ambulatory without ventilation vs £3,582 for non-ambulatory with ventilation		
	Outpatient: £1,398 per patient year for ambulatory vs £1,212 for non-ambulatory without ventilation vs £1,083 for non-ambulatory with ventilation		
	Accident and		

emergency: £55 per patient year for ambulatory vs £91 for non-ambulatory without ventilation vs £123 for non-ambulatory with ventilation

Inpatient admissions: £841 per patient year for ambulatory vs £3,221 for non-ambulatory without ventilation vs £3,531 for non-ambulatory with ventilation

Total costs: £2,931 per patient year for ambulatory vs £5,938 for non-ambulatory without ventilation vs £8,748 for non-ambulatory with ventilation

Healthcare costs by disease stage (2016-2020 only)

		Primary care: £162 per patient year for ambulatory (n=202) vs £269 for non-ambulatory without ventilation (n=116) vs £300 for non-ambulatory with ventilation (n=52) Prescriptions: £557 per patient year for ambulatory vs £1,259 for non-ambulatory without ventilation vs £3,360 for non-ambulatory with ventilation Outpatient: £1,732 per patient year for ambulatory vs £1,512 for non-ambulatory without ventilation vs £1,124 for non-ambulatory with ventilation Accident and emergency: £51 per

		patient year for ambulatory vs £101 for non-ambulatory without ventilation vs £164 for non-ambulatory with ventilation
		Inpatient admissions: £942 per patient year for ambulatory vs £3,229 for non-ambulatory without ventilation vs £5,547 for non-ambulatory with ventilation
		Total costs: £3,443 per patient year for ambulatory vs £6,370 for non-ambulatory without ventilation vs £10,494 for non-ambulatory with ventilation

Abbreviations: AE, adverse event; BNF, British National Formulary; DMD, Duchenne muscular dystrophy; DMDSAT, Duchenne muscular dystrophy functional ability Self-Assessment Tool; DS, disease stage; EA, early ambulatory; ECG, electrocardiogram; ED, emergency department; ENA, early non-ambulatory; GBP, great British pounds; GCC, glucocorticoid; GP, General Practitioner; HCP, healthcare professional; HCRU, healthcare resource utilisation; HST, highly specialised technology; ICU, intensive care unit; IQR, interquartile range; IRR, incidence rate ratio; LA, late ambulatory; LOA, loss of ambulation; LNA, late non-ambulatory; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NR, not reported; SD, standard deviation; SE, standard error; SMC, Scottish Medicines Consortium; UK, United Kingdom; yr, year

Appendix K. Published economic model studies

External literature for input to the health economic model

Identification and detection of relevant studies

An SLR was conducted to identify all published economic evaluations relevant to treatments in the management of patients with DMD. A comprehensive literature search was conducted following the standards set out in the PRISMA and Cochrane Handbook for Systematic Reviews of Interventions guidelines, as well as the rigorous standards required by NICE and most HTA agencies. The search strategy included a combination of MeSH or Emtree terms in addition to free-text terms for articles on human subjects published in English, covering economic evaluations, health-related quality of life (HRQoL), costs and healthcare resource use (HCRU). The searches were originally performed on 07 May 2024 for databases, and 09–13 May 2024 for congresses and HTA bodies. Further searches across any other sources were conducted on 10 June 2024. An update of the SLR was run in November 2024, with database searches on 07 November 2024, and hand searches on 06–08 November 2024.

Search strategy | electronic databases

The following electronic databases were searched:

- MEDLINE In-Process® (using pubmed.com)
- MEDLINE® and Embase® (using embase.com)
- National Institute for Health Research Economic Evaluation Database (NHS EED)
- Database of Abstracts of Reviews of Effects (DARE)
- International Health Technology Assessment Database (INAHTA)

Of note, the NHS EED and DARE was not searched in the SLR update. These databases have not been updated since 2015, so no relevant references would have been recovered by searching these again.

Where possible, all electronic databases were searched via their own respective platforms, or alternatively free to access hosting platforms. Details regarding which platforms were searched are provided in the titles for each search strategy.

For the original SLR, selected searches were restricted to the last 10 years to ensure that the submission reflected the most recent and relevant evidence for decision making. For the SLR update, searches were limited to the time since the prior SLR.

Table 51: Sources included in the search

Database	Platform/source	Relevant period for the search	Date of search completion

Embase	Embase.com	Full publication: 2014 to present Conference abstract: May 2022 to present	07.11.2024
Medline	Embase.com	Full publication: 2014 to present Conference abstract: May 2022 to present	07.11.2024
Medline In-process	https://pubmed.ncbi.nlm.nih.gov/	Full publication: 2014 to present Conference abstract: May 2022 to present	07.11.2024
NHS EED	www.crd.york.ac.uk/CRDWeb/	Full publication: 2014 to present Conference abstract: May 2022 to present	07.05.2024
DARE	www.crd.york.ac.uk/CRDWeb/	Full publication: 2014 to present Conference abstract: May 2022 to present	07.05.2024
INAHTA	https://www.inahta.org/hta-database/	Full publication: 2014 to present Conference abstract: May 2022 to present	07.05.2024

Abbreviations: NHS EED: National Institute for Health Research Economic Evaluation Database; DARE: Database of Abstracts of Reviews of Effects; INAHTA: International Health Technology Assessment Database

Original SLR | May 2024

The search strings used to identify relevant studies are provided in Table 116 for MEDLINE®, Table 117 for Embase®, Table 118 for DARE and NHS EED and Table 119 for INAHTA.

Table 116: Utilities, costs and HCRU, and economic evidence SLR | MEDLINE® via PubMed® | Searched 07 May 2024

#	Search terms	No. of hits
1	Disease string "Muscular Dystrophy, Duchenne"[MeSH] OR (("Duchenne"[Title/Abstract]) AND ("dystrophy"[Title/Abstract] OR "morbus"[Title/Abstract] OR "syndrome"[Title/Abstract] OR "muscular"[Title/Abstract])) OR	15,429

	"DMD"[Title/Abstract] NOT (("becker"[Title/Abstract]) OR ("Duchenne becker"[Title/Abstract]))	
2	Outcomes: QoL concepts "qaly*"[Title/Abstract] OR "quality adjusted life year*"[Title/Abstract] OR "quality-adjusted life year*"[Title/Abstract] OR "qale*"[Title/Abstract] OR "qtime*"[Title/Abstract] OR "daly*"[Title/Abstract] OR "disability-adjusted life year*"[Title/Abstract] OR "disability adjusted life year*"[Title/Abstract] OR "life-year*"[Title/Abstract] OR "life year*"[Title/Abstract] OR "disability-adjusted-life"[Title/Abstract] OR "disability-adjusted"[Title/Abstract] OR "quality-adjusted"[Title/Abstract] OR "quality-adjusted-life"[Title/Abstract] OR "hql"[Title/Abstract] OR "hqol"[Title/Abstract] OR "utilit*"[Title/Abstract] OR "disutilit*"[Title/Abstract] OR "willingness-to-pay"[Title/Abstract] OR "willingness to pay"[Title/Abstract] OR "wtp"[Title/Abstract] OR "standard-gamble*"[Title/Abstract] OR "time-trade-off"[Title/Abstract] OR "time-tradeoff"[Title/Abstract] OR "time tradeoff"[Title/Abstract] OR "time trade-off"[Title/Abstract] OR "time trade off"[Title/Abstract] OR "tto"[Title/Abstract] OR "carer quality of life"[Title/Abstract] OR "caregiver quality of life"[Title/Abstract] OR "carer burden"[Title/Abstract] OR "caregiver burden"[Title/Abstract] OR "parent quality of life"[Title/Abstract]	321,459
3	Outcomes: standard instruments "HUI"[Title/Abstract] OR "health utilities index"[Title/Abstract] OR "health utility index"[Title/Abstract] OR ("health-utilit*"[Title/Abstract] AND "index"[Title/Abstract]) OR "hui1"[Title/Abstract] OR "hui2"[Title/Abstract] OR "hui3"[Title/Abstract] OR "LSIA"[Title/Abstract] OR "life satisfaction index"[Title/Abstract] OR "euroqol"[Title/Abstract] OR "euro qol"[Title/Abstract] OR "euro-qol"[Title/Abstract] OR "eq-5d"[Title/Abstract] OR "eq5d"[Title/Abstract] OR "eq 5d"[Title/Abstract] OR "euroqual"[Title/Abstract] OR "euro qual"[Title/Abstract] OR "euro-qual"[Title/Abstract] OR "european quality of life 5 dimensions questionnaire"[Title/Abstract] OR "sf 6"[Title/Abstract] OR "sf6"[Title/Abstract] OR "sf-6"[Title/Abstract] OR "short-form-6"[Title/Abstract] OR "SF36"[Title/Abstract] OR "SF-36"[Title/Abstract] OR "SF 36"[Title/Abstract] OR "short form 36"[Title/Abstract] OR "shortform 36"[Title/Abstract] OR "short-form-36"[Title/Abstract] OR "shortform-36"[Title/Abstract] OR "visual analog scale"[Title/Abstract] OR "VAS"[Title/Abstract] OR "mapp*"[Title/Abstract]	424,954
4	#2 OR #3	733,098
5	Outcome: Costs and HCRU "budgets"[MeSH Terms] OR "resource allocation"[MeSH Terms] OR "Health Resources"[MeSH Terms] OR "Health Care Sector"[MeSH Terms] OR "Technology Assessment, Biomedical"[MeSH Terms] OR "economic*"[Title/Abstract] OR "cost"[Title/Abstract] OR "cost*"[Title/Abstract] OR "price"[Title/Abstract] OR "pric*"[Title/Abstract] OR "budget"[Title/Abstract] OR	1,458,987

	"budget*"[Title/Abstract] OR "pharmacoeconomic*"[Title/Abstract] OR "expenditure*"[Title/Abstract] OR "value for money"[Title/Abstract] OR (("resource"[Title/Abstract] OR "resourc*"[Title/Abstract]) AND ("use"[Title/Abstract] OR "utili*"[Title/Abstract])) OR "HCRU"[Title/Abstract] OR "Consumed resources"[Title/Abstract] OR "cost control"[Title/Abstract] OR "cost-control"[Title/Abstract]	
6	Outcome: Economic "Models, Economic"[MeSH] OR (("economic"[Title/Abstract] OR "economic*"[Title/Abstract]) AND ("model*"[Title/Abstract] OR "analysis"[Title/Abstract] OR "evaluation"[Title/Abstract])) OR (("model*"[Title/Abstract]) AND ("simulat*"[Title/Abstract] OR "area under curve"[Title/Abstract] OR "partition"[Title/Abstract] OR "transition*"[Title/Abstract] OR "state*"[Title/Abstract] OR "markov"[Title/Abstract] OR "cost effect*"[Title/Abstract] OR "cost utilit*"[Title/Abstract] OR "cost benefit*"[Title/Abstract] OR "cost-effect*"[Title/Abstract] OR "cost-utilit*"[Title/Abstract] OR "cost-benefit*"[Title/Abstract] OR "discrete event"[Title/Abstract] OR "markov"[Title/Abstract] OR "markov chain"[Title/Abstract] OR "decision tree"[Title/Abstract])) OR (("decision"[Title/Abstract]) AND ("analy*"[Title/Abstract] OR "tree*"[Title/Abstract])) OR "monte carlo simulation"[Title/Abstract] OR ("monte"[Title/Abstract] AND "carlo"[Title/Abstract]) OR "ICER"[Title/Abstract] OR "incremental cost effectiveness ratio"[Title/Abstract] OR "incremental cost-effectiveness ratio"[Title/Abstract] OR (("cost"[Title/Abstract]) AND ("effectiveness"[Title/Abstract] OR "benefit"[Title/Abstract] OR "utility"[Title/Abstract] OR "offset"[Title/Abstract] OR "analys*"[Title/Abstract])) OR (("cost*"[Title/Abstract]) AND ("variable*"[Title/Abstract] OR "unit*"[Title/Abstract] OR "estimate*"[Title/Abstract] OR "increment*"[Title/Abstract] OR "conseq*"[Title/Abstract] OR "minim*"[Title/Abstract] OR "offset"[Title/Abstract] OR "analys*"[Title/Abstract]))	1,486,706
7	Publication Type: Not required publications (e.g. Comment, Letter, Editorial, Case Reports, Guideline etc.) "case reports"[Publication Type] OR "editorial"[Publication Type] OR "letter"[Publication Type] OR "comment"[Publication Type] OR "clinical trial, veterinary"[Publication Type] OR "Guideline"[Publication Type] OR "News"[Publication Type] OR "Lecture"[Publication Type] OR "Interview"[Publication Type]	4,699,778
8	Publication Type: Not required publications (e.g. animal studies) "animals"[MeSH Terms] NOT ("animals"[MeSH Terms] AND "humans"[MeSH Terms])	5,217,863
9	#7 OR #8	9,786,315
10	Outcome: DMD + QoL	398

	(#1 AND #4) NOT #9	
11	Outcome: DMD + costs and HCRU (#1 AND #5) NOT #9	407
12	#11 | Last 10 years	277
13	Outcome: DMD + economic (#1 AND #6) NOT #9	459
14	#13 | Last 10 years	342
15	DMD + All outcomes #10 OR #12 OR #14	**815**

Table 117: Utilities, costs and HCRU, and economic evidence SLR | Embase® via embase.com | Searched 07 May 2024

#	Search terms	No. of hits
1	Disease string 'Duchenne muscular dystrophy'/syn OR (('duchenne':ti,ab,kw) AND ('dystrophy':ti,ab,kw OR 'morbus':ti,ab,kw OR 'syndrome':ti,ab,kw OR 'muscular':ti,ab,kw)) OR 'dmd':ti,ab,kw NOT (('becker':ti,ab,kw) OR ('duchenne becker':ti,ab,kw))	25,351
2	Outcomes: QoL concepts 'qaly*':ti,ab,kw OR 'quality adjusted life year*':ti,ab,kw OR 'quality-adjusted life year*':ti,ab,kw OR 'qale*':ti,ab,kw OR 'qtime*':ti,ab,kw OR 'daly*':ti,ab,kw OR 'disability-adjusted life year*':ti,ab,kw OR 'disability adjusted life year*':ti,ab,kw OR 'life-year*':ti,ab,kw OR 'life year*':ti,ab,kw OR 'disability-adjusted-life':ti,ab,kw OR 'disability-adjusted':ti,ab,kw OR 'quality-adjusted':ti,ab,kw OR 'quality-adjusted-life':ti,ab,kw OR 'utilit*':ti,ab,kw OR 'disutilit*':ti,ab,kw OR 'willingness-to-pay':ti,ab,kw OR 'willingness to pay':ti,ab,kw OR 'wtp':ti,ab,kw OR 'standard-gamble*':ti,ab,kw OR 'time-trade-off':ti,ab,kw OR 'time-tradeoff':ti,ab,kw OR 'time tradeoff':ti,ab,kw OR 'time trade-off':ti,ab,kw OR 'time trade off':ti,ab,kw OR 'tto':ti,ab,kw OR 'carer quality of life':ti,ab,kw OR 'caregiver quality of life':ti,ab,kw OR 'carer burden':ti,ab,kw OR 'caregiver burden':ti,ab,kw OR 'parent quality of life':ti,ab,kw	448,319
3	Outcomes: standard instruments 'hui':ti,ab,kw OR 'health utilities index':ti,ab,kw OR 'health utility index':ti,ab,kw OR ('health-utilit*':ti,ab,kw AND 'index':ti,ab,kw) OR 'hui1':ti,ab,kw OR 'hui2':ti,ab,kw OR 'hui3':ti,ab,kw OR 'lsia':ti,ab,kw OR 'life satisfaction index':ti,ab,kw OR 'euroqol':ti,ab,kw OR 'euro	559,747

	qol':ti,ab,kw OR 'euro-qol':ti,ab,kw OR 'eq-5d':ti,ab,kw OR 'eq5d':ti,ab,kw OR 'eq 5d':ti,ab,kw OR 'euroqual':ti,ab,kw OR 'euro qual':ti,ab,kw OR 'euro-qual':ti,ab,kw OR 'european quality of life 5 dimensions questionnaire':ti,ab,kw OR 'sf 6':ti,ab,kw OR 'sf6':ti,ab,kw OR 'sf-6':ti,ab,kw OR 'short-form-6':ti,ab,kw OR 'sf36':ti,ab,kw OR 'sf-36':ti,ab,kw OR 'sf 36':ti,ab,kw OR 'short form 36':ti,ab,kw OR 'shortform 36':ti,ab,kw OR 'short-form-36':ti,ab,kw OR 'shortform-36':ti,ab,kw OR 'visual analog scale':ti,ab,kw OR 'VAS':ti,ab,kw OR 'mapp*':ti,ab,kw	
4	#2 OR #3	987,091
5	Outcome: Costs and HCRU 'budget'/exp OR 'resource allocation'/exp OR 'health care planning'/exp OR 'health care cost'/exp OR 'biomedical technology assessment'/exp OR 'economic*':ti,ab,kw OR 'cost':ti,ab,kw OR 'cost*':ti,ab,kw OR 'price':ti,ab,kw OR 'pric*':ti,ab,kw OR 'budget':ti,ab,kw OR 'budget*':ti,ab,kw OR 'pharmacoeconomic*':ti,ab,kw OR 'expenditure*':ti,ab,kw OR 'value for money':ti,ab,kw OR (('resource':ti,ab,kw OR 'resourc*':ti,ab,kw) AND ('use':ti,ab,kw OR 'utili*':ti,ab,kw)) OR 'hcru':ti,ab,kw OR 'consumed resources':ti,ab,kw OR 'cost control':ti,ab,kw OR 'cost-control':ti,ab,kw	2,076,883
6	Outcome: Economic 'economic model'/exp OR (('economic':ti,ab,kw OR 'economic*':ti,ab,kw) AND ('model*':ti,ab,kw OR 'analysis':ti,ab,kw OR 'evaluation':ti,ab,kw) OR (('model*':ti,ab,kw) AND ('simulat*':ti,ab,kw OR 'area under curve':ti,ab,kw OR 'partition':ti,ab,kw OR 'transition*':ti,ab,kw OR 'state*':ti,ab,kw OR 'markov':ti,ab,kw) OR 'cost effect*':ti,ab,kw OR 'cost utilit*':ti,ab,kw OR 'cost benefit*':ti,ab,kw OR 'cost-effect*':ti,ab,kw OR 'cost-utilit*':ti,ab,kw OR 'cost-benefit*':ti,ab,kw OR 'discrete event':ti,ab,kw OR 'markov':ti,ab,kw OR 'markov chain':ti,ab,kw OR 'decision tree':ti,ab,kw)) OR (('decision':ti,ab,kw) AND ('analy*':ti,ab,kw OR 'tree*':ti,ab,kw)) OR 'monte carlo simulation':ti,ab,kw OR ('monte':ti,ab,kw AND 'carlo':ti,ab,kw) OR 'icer':ti,ab,kw OR 'incremental cost effectiveness ratio':ti,ab,kw OR 'incremental cost-effectiveness ratio':ti,ab,kw OR (('cost':ti,ab,kw) AND ('effectiveness':ti,ab,kw OR 'benefit':ti,ab,kw OR 'utility':ti,ab,kw OR 'offset':ti,ab,kw OR 'analys*':ti,ab,kw)) OR (('cost*':ti,ab,kw) AND ('variable*':ti,ab,kw OR 'unit*':ti,ab,kw OR 'estimate*':ti,ab,kw OR 'increment*':ti,ab,kw OR 'conseq*':ti,ab,kw OR 'minim*':ti,ab,kw OR 'offset':ti,ab,kw OR 'analys*':ti,ab,kw))	1,925,792
7	Publication Type: Not required publications (e.g. Comment, Letter, Editorial, Case Reports, Guideline etc.) 'case reports':it OR 'editorial':it OR 'letter':it OR 'comment':it OR 'clinical trial, veterinary':it OR 'guideline':it OR 'news':it OR 'lecture':it OR 'interview':it	2,109,870
8	Publication Type: Not required publications (e.g. animal studies)	6,120,557

	'animal'/exp NOT ('animal'/exp AND 'human'/exp)	
9	#7 OR #8	8,188,468
10	Outcome: DMD + QoL (#1 AND #4) NOT #9	760
11	Outcome: DMD + Costs/HCRU (#1 AND #5) NOT #9	977
12	#11 | Last 10 years	679
13	Outcome: DMD + Economic (#1 AND #6) NOT #9	935
14	#13 | Last 10 years	679
15	Outcome: All outcomes #10 OR #12 OR #14	**1,641**

Table 118: Utilities, costs and HCRU, and economic evidence SLR | DARE & NHS EED (via CRD for DARE) | Searched 07 May 2024

#	Search terms	No. of hits
1	"Muscular Dystrophy, Duchenne"[MeSH Terms] OR (("Duchenne"[any field] AND ("dystrophy"[any field] OR "morbus"[any field] OR "syndrome"[any field])) OR "DMD"[any field] NOT ("becker"[any field] OR "Duchenne becker"[any field])	**31**

Table 119: Utilities, costs and HCRU, and economic evidence SLR | HTAD via INAHTA | Searched 07 May 2024

#	Search terms	No. of hits
1	"Muscular Dystrophy, Duchenne"[MeSH Terms] (("Duchenne"[any field] AND ("dystrophy"[any field] OR "morbus"[any field] OR "syndrome"[any field])) OR "DMD"[any field]	**15**

SLR Update | November 2024

The search strings used to identify relevant studies are provided in Table 120 for MEDLINE®, Table 121 for Embase® and Table 122 for INAHTA.

Table 120 | Utilities, costs and HCRU, and economic evidence SLR | MEDLINE® via PubMed® | Searched 07 November 2024

#	Search terms	No. of hits
1	Disease string "Muscular Dystrophy, Duchenne"[Mesh] OR (("Duchenne"[Title/Abstract]) AND ("dystrophy"[Title/Abstract] OR "morbus"[Title/Abstract] OR "syndrome"[Title/Abstract] OR "muscular"[Title/Abstract])) OR "DMD"[Title/Abstract] NOT (("becker"[Title/Abstract]) OR ("Duchenne becker"[Title/Abstract]))	15, 831
2	Outcomes: QoL concepts "qaly*"[Title/Abstract] OR "quality adjusted life year*"[Title/Abstract] OR "quality-adjusted life year*"[Title/Abstract] OR "qale*"[Title/Abstract] OR "qtime*"[Title/Abstract] OR "daly*"[Title/Abstract] OR "disability-adjusted life year*"[Title/Abstract] OR "disability adjusted life year*"[Title/Abstract] OR "life-year*"[Title/Abstract] OR "life year*"[Title/Abstract] OR "disability-adjusted-life"[Title/Abstract] OR "disability-adjusted"[Title/Abstract] OR "quality-adjusted"[Title/Abstract] OR "quality-adjusted-life"[Title/Abstract] OR "hql"[Title/Abstract] OR "hqol"[Title/Abstract] OR "utilit*"[Title/Abstract] OR "disutilit*"[Title/Abstract] OR "willingness-to-pay"[Title/Abstract] OR "willingness to pay"[Title/Abstract] OR "wtp"[Title/Abstract] OR "standard-gamble*"[Title/Abstract] OR "time-trade-off"[Title/Abstract] OR "time-tradeoff"[Title/Abstract] OR "time tradeoff"[Title/Abstract] OR "time trade-off"[Title/Abstract] OR "time trade off"[Title/Abstract] OR "tto"[Title/Abstract] OR "carer quality of life"[Title/Abstract] OR "caregiver quality of life"[Title/Abstract] OR "carer burden"[Title/Abstract] OR "caregiver burden"[Title/Abstract] OR "parent quality of life"[Title/Abstract]	335,859
3	Outcomes: standard instruments "HUI"[Title/Abstract] OR "health utilities index"[Title/Abstract] OR "health utility index"[Title/Abstract] OR ("health-utilit*"[Title/Abstract] AND "index"[Title/Abstract]) OR "hui1"[Title/Abstract] OR "hui2"[Title/Abstract] OR "hui3"[Title/Abstract] OR "LSIA"[Title/Abstract] OR "life satisfaction index"[Title/Abstract] OR "euroqol"[Title/Abstract] OR "euro qol"[Title/Abstract] OR "euro-qol"[Title/Abstract] OR "eq-5d"[Title/Abstract] OR "eq5d"[Title/Abstract] OR "eq 5d"[Title/Abstract] OR "euroqual"[Title/Abstract] OR "euro qual"[Title/Abstract] OR "euro-qual"[Title/Abstract] OR "european quality of life 5 dimensions questionnaire"[Title/Abstract] OR "sf 6"[Title/Abstract] OR "sf6"[Title/Abstract] OR "sf-6"[Title/Abstract] OR "short-form-6"[Title/Abstract] OR "SF36"[Title/Abstract] OR "SF-36"[Title/Abstract] OR "SF 36"[Title/Abstract] OR "short form 36"[Title/Abstract] OR "shortform 36"[Title/Abstract] OR "short-form-36"[Title/Abstract] OR "shortform-36"[Title/Abstract] OR "visual analog scale"[Title/Abstract] OR "VAS"[Title/Abstract] OR "mapp*"[Title/Abstract]	439, 967

4	#2 OR #3	761,946
5	Outcome: Costs and HCRU "budgets"[MeSH Terms] OR "resource allocation"[MeSH Terms] OR "Health Resources"[MeSH Terms] OR "Health Care Sector"[MeSH Terms] OR "Technology Assessment, Biomedical"[MeSH Terms] OR "economic*"[Title/Abstract] OR "cost"[Title/Abstract] OR "cost*"[Title/Abstract] OR "price"[Title/Abstract] OR "pric*"[Title/Abstract] OR "budget"[Title/Abstract] OR "budget*"[Title/Abstract] OR "pharmacoeconomic*"[Title/Abstract] OR "expenditure*"[Title/Abstract] OR "value for money"[Title/Abstract] OR (("resource"[Title/Abstract] OR "resourc*"[Title/Abstract]) AND ("use"[Title/Abstract] OR "utili*"[Title/Abstract])) OR "HCRU"[Title/Abstract] OR "Consumed resources"[Title/Abstract] OR "cost control"[Title/Abstract] OR "cost-control"[Title/Abstract]	1,516,209
6	Outcome: Economic "Models, Economic"[Mesh] OR (("economic"[Title/Abstract] OR "economic*"[Title/Abstract]) AND ("model*"[Title/Abstract] OR "analysis"[Title/Abstract] OR "evaluation"[Title/Abstract])) OR (("model*"[Title/Abstract]) AND ("simulat*"[Title/Abstract] OR "area under curve"[Title/Abstract] OR "partition"[Title/Abstract] OR "transition*"[Title/Abstract] OR "state*"[Title/Abstract] OR "markov"[Title/Abstract] OR "cost effect*"[Title/Abstract] OR "cost utilit*"[Title/Abstract] OR "cost benefit*"[Title/Abstract] OR "cost-effect*"[Title/Abstract] OR "cost-utilit*"[Title/Abstract] OR "cost-benefit*"[Title/Abstract] OR "discrete event"[Title/Abstract] OR "markov"[Title/Abstract] OR "markov chain"[Title/Abstract] OR "decision tree"[Title/Abstract])) OR (("decision"[Title/Abstract]) AND ("analy*"[Title/Abstract] OR "tree*"[Title/Abstract])) OR "monte carlo simulation"[Title/Abstract] OR ("monte"[Title/Abstract] AND "carlo"[Title/Abstract]) OR "ICER"[Title/Abstract] OR "incremental cost effectiveness ratio"[Title/Abstract] OR "incremental cost-effectiveness ratio"[Title/Abstract] OR (("cost"[Title/Abstract]) AND ("effectiveness"[Title/Abstract] OR "benefit"[Title/Abstract] OR "utility"[Title/Abstract] OR "offset"[Title/Abstract] OR "analys*"[Title/Abstract])) OR (("cost*"[Title/Abstract]) AND ("variable*"[Title/Abstract] OR "unit*"[Title/Abstract] OR "estimate*"[Title/Abstract] OR "increment*"[Title/Abstract] OR "conseq*"[Title/Abstract] OR "minim*"[Title/Abstract] OR "offset"[Title/Abstract] OR "analys*"[Title/Abstract]))	1,554,341
7	Publication Type: Not required publications (e.g. Comment, Letter, Editorial, Case Reports, Guideline etc.) "case reports"[Publication Type] OR "editorial"[Publication Type] OR "letter"[Publication Type] OR "comment"[Publication Type] OR "clinical trial, veterinary"[Publication Type] OR "Guideline"[Publication Type] OR "News"[Publication Type] OR "Lecture"[Publication Type] OR "Interview"[Publication Type]	4,790,240

8	Publication Type: Not required publications (e.g. animal studies) "animals"[MeSH Terms] NOT ("animals"[MeSH Terms] AND "humans"[MeSH Terms])	5,272,703
9	#7 OR #8	9,930,215
10	Outcome: DMD + QoL (#1 AND #4) NOT #9	414
11	#10 AND 2024/5/7:3000/12/12[pdat]	18
12	Outcome: DMD + costs and HCRU (#1 AND #5) NOT #9	427
13	#12 AND 2024/5/7:3000/12/12[pdat]	22
14	Outcome: DMD + economic (#1 AND #6) NOT #9	488
15	#14 AND 2024/5/7:3000/12/12[pdat]	33
16	DMD + All outcomes #11 OR #13 OR #15	**54**

Table 121 | Utilities, costs and HCRU, and economic evidence SLR | Embase® via embase.com | Searched 07 November 2024

#	Search terms	No. of hits
1	Disease string 'Duchenne muscular dystrophy'/syn OR (('duchenne':ti,ab,kw) AND ('dystrophy':ti,ab,kw OR 'morbus':ti,ab,kw OR 'syndrome':ti,ab,kw OR 'muscular':ti,ab,kw)) OR 'dmd':ti,ab,kw NOT (('becker':ti,ab,kw) OR ('duchenne becker':ti,ab,kw))	26,242
2	Outcomes: QoL concepts 'qaly*':ti,ab,kw OR 'quality adjusted life year*':ti,ab,kw OR 'quality-adjusted life year*':ti,ab,kw OR 'qale*':ti,ab,kw OR 'qtime*':ti,ab,kw OR 'daly*':ti,ab,kw OR 'disability-adjusted life year*':ti,ab,kw OR 'disability adjusted life year*':ti,ab,kw OR 'life-year*':ti,ab,kw OR 'life year*':ti,ab,kw OR 'disability-adjusted-life':ti,ab,kw OR 'disability-adjusted':ti,ab,kw OR 'quality-adjusted':ti,ab,kw OR 'quality-adjusted-life':ti,ab,kw OR 'utilit*':ti,ab,kw OR 'disutilit*':ti,ab,kw OR 'willingness-to-pay':ti,ab,kw OR 'willingness to pay':ti,ab,kw OR 'wtp':ti,ab,kw OR 'standard-gamble*':ti,ab,kw OR 'time-trade-off':ti,ab,kw OR 'time-tradeoff':ti,ab,kw OR 'time tradeoff':ti,ab,kw OR 'time trade-off':ti,ab,kw OR 'time trade off':ti,ab,kw OR 'tto':ti,ab,kw OR 'carer quality of life':ti,ab,kw OR 'caregiver quality of	466,262

	life':ti,ab,kw OR 'carer burden':ti,ab,kw OR 'caregiver burden':ti,ab,kw OR 'parent quality of life':ti,ab,kw	
3	Outcomes: standard instruments 'hui':ti,ab,kw OR 'health utilities index':ti,ab,kw OR 'health utility index':ti,ab,kw OR ('health-utilit*':ti,ab,kw AND 'index':ti,ab,kw) OR 'hui1':ti,ab,kw OR 'hui2':ti,ab,kw OR 'hui3':ti,ab,kw OR 'lsia':ti,ab,kw OR 'life satisfaction index':ti,ab,kw OR 'euroqol':ti,ab,kw OR 'euro qol':ti,ab,kw OR 'euro-qol':ti,ab,kw OR 'eq-5d':ti,ab,kw OR 'eq5d':ti,ab,kw OR 'eq 5d':ti,ab,kw OR 'euroqual':ti,ab,kw OR 'euro qual':ti,ab,kw OR 'euro-qual':ti,ab,kw OR 'european quality of life 5 dimensions questionnaire':ti,ab,kw OR 'sf 6':ti,ab,kw OR 'sf6':ti,ab,kw OR 'sf-6':ti,ab,kw OR 'short-form-6':ti,ab,kw OR 'sf36':ti,ab,kw OR 'sf-36':ti,ab,kw OR 'sf 36':ti,ab,kw OR 'short form 36':ti,ab,kw OR 'shortform 36':ti,ab,kw OR 'short-form-36':ti,ab,kw OR 'shortform-36':ti,ab,kw OR 'visual analog scale':ti,ab,kw OR 'VAS':ti,ab,kw OR 'mapp*':ti,ab,kw	577,878
4	#2 OR #3	1,022,400
5	Outcome: Costs and HCRU 'budget'/exp OR 'resource allocation'/exp OR 'health care planning'/exp OR 'health care cost'/exp OR 'biomedical technology assessment'/exp OR 'economic*':ti,ab,kw OR 'cost':ti,ab,kw OR 'cost*':ti,ab,kw OR 'price':ti,ab,kw OR 'pric*':ti,ab,kw OR 'budget':ti,ab,kw OR 'budget*':ti,ab,kw OR 'pharmacoeconomic*':ti,ab,kw OR 'expenditure*':ti,ab,kw OR 'value for money':ti,ab,kw OR (('resource':ti,ab,kw OR 'resourc*':ti,ab,kw) AND ('use':ti,ab,kw OR 'utili*':ti,ab,kw)) OR 'hcru':ti,ab,kw OR 'consumed resources':ti,ab,kw OR 'cost control':ti,ab,kw OR 'cost-control':ti,ab,kw	2,145,789
6	Outcome: Economic 'economic model'/exp OR (('economic':ti,ab,kw OR 'economic*':ti,ab,kw) AND ('model*':ti,ab,kw OR 'analysis':ti,ab,kw OR 'evaluation':ti,ab,kw) OR (('model*':ti,ab,kw) AND ('simulat*':ti,ab,kw OR 'area under curve':ti,ab,kw OR 'partition':ti,ab,kw OR 'transition*':ti,ab,kw OR 'state*':ti,ab,kw OR 'markov':ti,ab,kw) OR 'cost effect*':ti,ab,kw OR 'cost utilit*':ti,ab,kw OR 'cost benefit*':ti,ab,kw OR 'cost-effect*':ti,ab,kw OR 'cost-utilit*':ti,ab,kw OR 'cost-benefit*':ti,ab,kw OR 'discrete event':ti,ab,kw OR 'markov':ti,ab,kw OR 'markov chain':ti,ab,kw OR 'decision tree':ti,ab,kw)) OR (('decision':ti,ab,kw) AND ('analy*':ti,ab,kw OR 'tree*':ti,ab,kw)) OR 'monte carlo simulation':ti,ab,kw OR ('monte':ti,ab,kw AND 'carlo':ti,ab,kw) OR 'icer':ti,ab,kw OR 'incremental cost effectiveness ratio':ti,ab,kw OR 'incremental cost-effectiveness ratio':ti,ab,kw OR (('cost':ti,ab,kw) AND ('effectiveness':ti,ab,kw OR 'benefit':ti,ab,kw OR 'utility':ti,ab,kw OR 'offset':ti,ab,kw OR 'analys*':ti,ab,kw)) OR (('cost*':ti,ab,kw) AND ('variable*':ti,ab,kw OR 'unit*':ti,ab,kw OR 'estimate*':ti,ab,kw OR 'increment*':ti,ab,kw OR 'conseq*':ti,ab,kw OR 'minim*':ti,ab,kw OR 'offset':ti,ab,kw OR 'analys*':ti,ab,kw))	2,004,988
7	Publication Type: Not required publications (e.g. Comment, Letter, Editorial, Case Reports, Guideline etc.) 'case reports':it OR 'editorial':it OR 'letter':it OR 'comment':it OR 'clinical trial, veterinary':it OR 'guideline':it OR 'news':it OR 'lecture':it OR 'interview':it	2,153,091
8	Publication Type: Not required publications (e.g. animal studies)	6,202,877

	'animal'/exp NOT ('animal'/exp AND 'human'/exp)	
9	#7 OR #8	8,313,477
10	Outcome: DMD + QoL (#1 AND #4) NOT #9	797
11	#10 AND [07-05-2024]/sd NOT [02-12-2024]/sd	41
12	Outcome: DMD + Costs/HCRU (#1 AND #5) NOT #9	1,048
13	#12 AND [07-05-2024]/sd NOT [02-12-2024]/sd	75
14	Outcome: DMD + Economic (#1 AND #6) NOT #9	1,002
15	#14 AND [07-05-2024]/sd NOT [02-12-2024]/sd	73
16	Outcome: All outcomes #11 OR #13 OR #15	**144**

Table 122 | Utilities, costs and HCRU, and economic evidence SLR | HTAD via INAHTA | Searched 07 November 2024

#	Search terms	No. of hits
1	"Muscular Dystrophy, Duchenne"[MeSH Terms] OR (("Duchenne"[any field] AND ("dystrophy"[any field] OR "morbus"[any field] OR "syndrome"[any field])) OR "DMD"[any field]	**17**
2	#1 | From date of original SLR search to current	**1**

Search strategy | Hand searching

Hand searching supplemented the electronic database searches. Firstly, published SLRs and NMAs that were identified in database searches were reviewed as a supplemental source to identify relevant primary publications. Secondly, to identify further studies not captured in the electronic database searches, proceedings of relevant congresses held between 2022–2024 (inclusive) were searched via the conferences' online platforms, or via downloadable abstract books. Finally, HTA bodies were reviewed to identify evidence from the last 10 years not captured in the electronic database searches. Hand searches

were repeated between 06-08 November 2024 to identify any new publications since the original SLR. The sources examined are described below.

Congresses

The following congresses were searched:

- Global/international congresses:
- Annual Congress of the World Muscle Society
- International Congress of Neuropathology
- Action Duchenne Annual International Conference, linked with the DMD registry part of the TREAT-NMD Global Registries
- TREAT-NMD International Conference
- International Pediatric Summit
- MDA conference
- Health Technology Assessment International (HTAi)
- Academy of Managed Care Pharmacy (AMCP)
- International society for quality of life research (ISOQOL)
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR)

Europe and UK congresses:

- British Paediatric Neurology Association Annual Conference
- Myology Congress
- EPNS

HTA bodies

The following HTA agencies were also searched:

- NICE
- SMC
- NCPE
- ICER
- EUnetHTA
- CADTH
- PBAC
- TGA

Other sources

The following other sources were also searched for relevant data from the last 10 years to identify linked publications and additional studies not identified in the electronic database searches:

- Government/International bodies: Duchenne UK, Action Duchenne, NIHR Innovation Observatory, NIHR UK Journals Library, Agency for Healthcare Research and Quality and NICE evidence summaries

- Additional sources included: cost-effectiveness analysis (CEA) registry, RePEc website, EQ-5D website, ScHARRHUD database, Health economics research centres (HERC)-maintained mapping algorithm database, Library of Digital Endpoints.

Original SLR

The search terms used for the hand searches were simple, focussing on different disease names or key terms relevant to the SLRs. The search terms used for the congress searches are provided in Table 123, HTA searches in Table 124 and additional sources in Table 125.

Table 123 | Congress searches | Searched 09-13 May 2024

Congress	Year	Search terms	Hits per search	Total hits
Annual Congress of the World Muscle Society	2022	Utilit	3	10
		5D	1	
		Cost	6	
		Resource	0	
	2023	Utilit	0	9
		5D	0	
		Cost	8	
		Resource	1	
International Congress of Neuropathology*	2023	Utilit	0	0
		5D	0	
		Cost	0	
		Resource	0	
Action Duchenne Annual International Conference	2022	Utilit	0	4
		5D	0	
		Cost	1	

		Resource	3	
	2023	Utilit	0	0
		5D	0	
		Cost	0	
		Resource	0	
TREAT-NMD International Conference	No proceedings available online	N/A	N/A	N/A
International Pediatric Summit†	2023	Utilit	0	0
		5D	0	
		Cost	0	
		Resource	0	
	2024	Utilit	1	1
		5D	0	
		Cost	0	
		Resource	0	
Muscular dystrophy association (MDA) conference	2022	Utilit	0	24
		5D	1	
		Cost	12	
		Resource	11	
	2023	Utilit	0	18
		5D	1	
		Cost	8	
		Resource	9	

	2024	Utilit	0	24
		5D	4	
		Cost	12	
		Resource	8	
British Paediatric Neurology Association Annual Conference	2022	Utilit	0	0
		5D	0	
		Cost	0	
		Resource	0	
	2023	Utilit	0	0
		5D	0	
		Cost	0	
		Resource	0	
	2024	Utilit	0	0
		5D	0	
		Cost	0	
		Resource	0	
Myology congress	2022**	Utilit	0	0
		5D	0	
		Cost	0	
		Resource	0	
	2024††	Utilit	2	30
		5D	5	
		Cost	21	

		Resource	2	
Congress of the European Paediatric Neurology Society (EPNS)	2022	Utilit	0	0
		5D	0	
		Cost	0	
		Resource	0	
	2023	Utilit	14	60
		5D	3	
		Cost	33	
		Resource	10	
Health Technology Assessment International (HTAi)	2022 2023	Duchenne muscular dystrophy	0	0
		DMD	0	
		Duchenne	0	
Academy of Managed Care Pharmacy (AMCP)	2022 2023	Duchenne muscular dystrophy	0	0
		DMD	0	
		Duchenne	0	
International society for quality of life research (ISOQOL)	2022 2023	Duchenne muscular dystrophy	0	0
		DMD	0	
		Duchenne	0	
International Society for Pharmacoeconomics and Outcomes Research (ISPOR)	Results filter for 2022, 2023, and 2024 congresses in Europe and US	DMD OR (Duchenne AND muscular AND dystrophy)	2022 USA: 10 2022 Europe: 11	70

		2023 USA: 14 2023 Europe: 18 2024 USA: 17
Total		250

Notes: Congresses were searched through the "Find" option on the PDFs or online recordings available, since no search bar was available, with the exception of the MDA conference, the HTAi conference, and ISPOR, which were searched through the available search bar.
*Only the 2023 congress was searched, since the International Congress of Neuropathology takes place every 4 years; †The 2022 agenda was only found in Arabic and was, therefore, not searched; **Abstract book not freely available online; ††No 2023 congress identified.
Abbreviations: DMD, Duchenne muscular dystrophy; HTAi, Health Technology Assessment International; ISPOR, International Society for Pharmacoeconomics and Outcomes Research; MDA, Muscular dystrophy association; N/A, not applicable

Table 124 | HTA searches | Searched 13 May 2024

HTA body	Search terms	Total hits
NICE	Duchenne Muscular Dystrophy Last 10 years	16
SMC		3
NCPE		0
ICER		10
EUnetHTA		0
CDA		5
PBAC		0
TGA		5
Total		39

Abbreviations: CDA, Canada's Drug Agency; EU, European Unionl; HTA, Health technology assessment; ICER, Institute for Clinical and Economic Review; NCPE, National Centre for Pharmacoeconomics Ireland; NICE, National Institute of Health and Care Excellence; PBAC, Pharmaceutical benefits advisory committee; SLR, systematic literature review; SMC, Scottish Medicines Consortium; TGA, therapeutic goods administration

Table 125 | Additional searches | Searched 13 May – 12 June 2024

Source	Search terms	Total hits	Additional hits
NIHR Innovation Observatory	Duchenne Muscular Dystrophy Last 10 years	7	0
NIHR UK Journals Library		19	0
Agency for Healthcare Research and Quality		12	0
Duchenne UK	Cost Utilit Economic	0	-
Action Duchenne		0	-
NICE evidence summaries	Duchenne muscular dystrophy	0	-
CEA registry	Duchenne muscular dystrophy Last 10 years	Methods: 3 Ratios: 2 Utilities: 2	7
RePEc website via IDEAS		89	89
EQ-5D website		0	-
ScHARRHUD database		2	2
HERC-maintained mapping algorithm database		0	-
Library of Digital Endpoints		1	1
Total			99

Abbreviations: CEA, cost-effectiveness analysis; HERC, Health economics centre; NICE, National Institute for Health and Care Excellence; NIHR, National Institute for Health and Care Research; RePEc, research papers

in economics; ScHARRHUD, School of Health and Related Research Health Utilities Database; UK, United Kingdom

SLR Update

The search terms used for update SLR were the same as for the original SLR. The search terms used for the congress searches are provided in Table 126, HTA searches in Table 127 and additional sources in Table 128.

Table 126 | Congress searches | Searched 06 November 2024

Congress	Search terms	Hits per search	Total hits
Annual Congress of the World Muscle Society	Utilit	4	10
	5D	1	
	cost	1	
	resource	4	
International Congress of Neuropathology	As above	N/A	N/A
Action Duchenne Annual International Conference	As above	N/A	N/A
TREAT-NMD International Conference	As above	N/A	N/A
International Pediatric Summit	As above	N/A	N/A
Muscular dystrophy association (MDA) conference	As above	N/A	N/A
British Paediatric Neurology Association Annual Conference	As above	N/A	N/A
Myology congress	As above	N/A	N/A

Congress of the European Paediatric Neurology Society (EPNS)	As above	N/A	N/A
Health Technology Assessment International (HTAi)*	Duchenne muscular dystrophy	0	0
	DMD	0	
	Duchenne	0	
Academy of Managed Care Pharmacy (AMCP)	Duchenne muscular dystrophy	7	18
	DMD	4	
	Duchenne	7	
International society for quality of life research (ISOQOL)	Duchenne muscular dystrophy	2	6
	DMD	2	
	Duchenne	2	
International Society for Pharmacoeconomics and Outcomes Research (ISPOR)	DMD OR (Duchenne AND muscular AND dystrophy)	N/A	N/A
Total			34

Notes: *A programme was found for the congress via the website, however there was no readily available search function and so it was not searched further. Congresses have been searched through the "Find" option on the PDFs found via the congress websites; either abstract booklets or programmes (if the latter then only titles were searched, otherwise both titles and abstracts were searched, but author affiliations were not).

Abbreviations: DMD, Duchenne muscular dystrophy; N/A, not applicable

Table 127 | HTA Searches | Searched 06 November 2024

HTA body	Search terms	Total hits

NICE	Duchenne Muscular Dystrophy	0 (4)*
SMC		0
NCPE		0
ICER		0
EUnetHTA		0
CDA		0
PBAC		0
TGA		1
Total		1

Notes: *Guidance in development – not included in the SLR

Abbreviations: CDA, Canada's Drug Agency; EUnetHTA, European Network for Health Technology Assessment; HTA, Health technology assessment; ICER, Institute for Clinical and Economic Review; NCPE, National Centre for Pharmacoeconomics Ireland; NICE, National Institute of Health and Care Excellence; PBAC, Pharmaceutical benefits advisory committee; SLR, systematic literature review; SMC, Scottish Medicines Consortium; TGA, therapeutic goods administration

Table 128 | Additional searches | Searched 06-08 November 2024

Source	Search terms	Total hits
Duchenne UK	Cost Utilit Economic	0
Action Duchenne	Cost	2
	Utilit	0
	Economic	0
NIHR Innovation Observatory	Duchenne muscular dystrophy	0
NIHR UK Journals Library		0

Agency for Healthcare Research and Quality	0
NICE evidence summaries	0
CEA registry	0
RePEc website via IDEAS	9
EQ-5D website	1
ScHARRHUD database	0
HERC-maintained mapping algorithm database	0
Library of Digital Endpoints	0
Total	12

Abbreivations: CEA, cost-effectiveness analysis; HERC, Health economics centre; NICE, National Institute for Health and Care Excellence; NIHR, National Institute for Health and Care Research; RePEc, research papers in economics; ScHARRHUD, School of Health and Related Research Health Utilities Database; UK, United Kingdom.

Study selection

The search results were exported to EndNote and de-duplicated. Each publication was then screened against pre-defined eligibility (inclusion and exclusion) PICOS criteria, in Microsoft Excel® to establish which studies were eligible for inclusion. Initially, citations were screened by title and abstract (first-pass stage). Each citation was screened by two independent reviewers and any discrepancies between the reviewers were reconciled through consensus or a third independent reviewer. Citations that did not match the eligibility criteria, and duplicate citations owing to overlap in the coverage of databases, were excluded at the first-pass stage; wherever unclear, citations were included. Full-text articles were retrieved for potentially relevant studies that were eligible after first-pass screening. Each full text was screened by two independent reviewers, using the same pre-defined eligibility PICOS criteria, and any discrepancies between reviewers were reconciled by a third independent reviewer.

Eligibility criteria

The prespecified eligibility criteria for cost-effectiveness studies are detailed in Table 129. The same eligibility criteria were used for the update SLR, notwithstanding 'date of publication' which was from the date or the prior SLR to present.

Table 129: Economic model studies SLR | Eligibility (PICOS) criteria

	Inclusion criteria	Exclusion criteria
Population	Patients with a diagnosis of DMD	Other muscular dystrophies including Becker muscular dystrophy
Intervention/ comparator	Any	None
Outcomes	• Economic evaluations (models and trial-based) • Model summary (including perspective, time horizon and discounting) and structure, where applicable • Assumptions underpinning model structures • Estimation of transition probabilities and uncertainty • Key cost drivers • Sources of clinical, cost and QoL inputs • Discounting of costs and health outcomes • Summary health outcomes (e.g. QALYs, DALYs, LYG) • ICERs: cost per QALY/DALY/LYG, cost per event avoided • Range of ICERs as per probabilistic/deterministic sensitivity analyses, e.g. subgroups explored • PROs: • Utilities derived using generic preference-based instruments (e.g. EQ-5D, SF-6D, HUI2, HUI3, QoL) for relevant health states • Direct utility estimates (e.g. standard gamble, time trade off, discrete choice experiment) • Mapping studies, from disease-specific to generic preference-based measures or between different generic preference-based measures • Descriptive summary of health states, and/or change in health status/QoL results	N/A

Study design	Economic evaluations–trial-based and economic models including: • CEA • CUA • CMA • CCA • CBA • COA • Economic Evaluation alongside Clinical Trials	• Non-systematic reviews • Editorials, comments, letters, case reports, case series • Animal studies • Burden of illness studies
Language	English only	Non-English
Date of publication	Full publication: 2014 to present Conference abstract: May 2022 to present	None
Countries	No restriction	None

Abbreviations: CBA, cost-benefit analysis; CCA, cost-consequence analysis; CEA, cost-effectiveness analysis; CMA, cost-minimisation analysis; COA, cost-offset analysis; CUA, cost-utility analysis; DALY, disability-adjusted life year; DMD, Duchenne muscular dystrophy; HUI, health-utility index; ICER, Incremental cost effectiveness ratio; LYG, life years gained; N/A, not applicable; PRO, patient-reported outcome; QALY, quality-adjusted life year; QoL, quality of life; SF-6D, short-form 6-dimension; SLR, systematic literature review.

Data extraction and quality assessment

Relevant data from included studies were inserted into extraction tables in Microsoft Excel®. Data were extracted by one reviewer and spot-checked for quality by a second reviewer; if necessary, discrepancies were reconciled by a third reviewer. The outcomes of the included studies are presented in Appendix K.

Results

Prisma flow diagram

For the original SLR of the 2,502 papers identified for the cost-effectiveness, health-related quality of life (Appendix I), and costs and resource use (Appendix J) SLRs by the database searches, 552 were removed as duplicates, and the titles and abstracts of 1,950 papers were reviewed for the cost-effectiveness SLR at first-pass screening. After exclusion of 1,871 papers, the full texts of 79 publications were reviewed at second-pass screening, of which 68 were subsequently excluded. A total of 11 papers met the pre-defined inclusion criteria from the database searches and were included in the cost-effectiveness review.

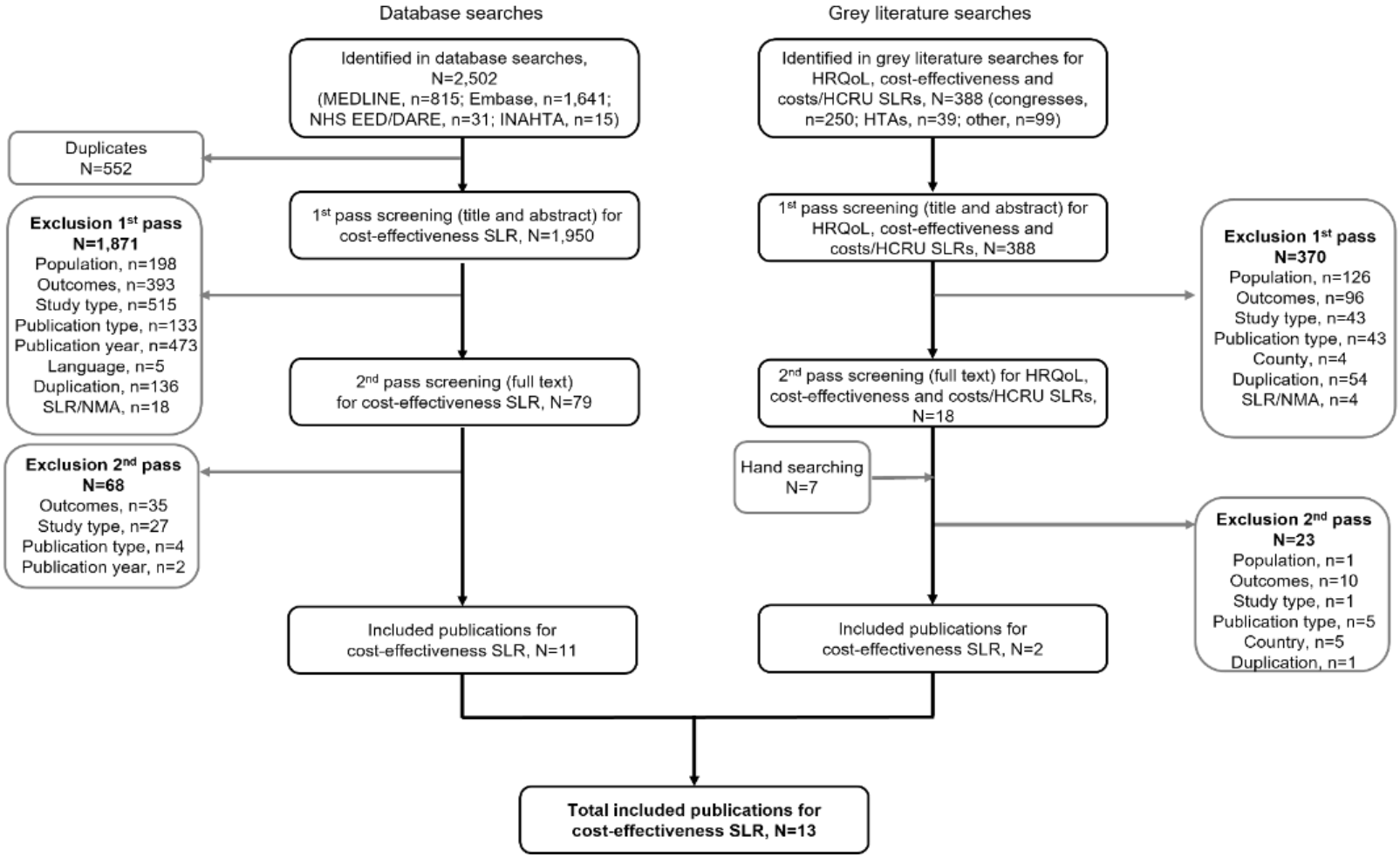
Of the 388 publications identified for the cost-effectiveness, HRQoL, and costs and resource use SLRs by grey literature searching, 370 were excluded following first-pass

screening. Additionally, seven publications were identified through hand searching. Of the 25 publications, that were reviewed as full-text articles, 23 were excluded and two met the selection criteria for inclusion in the cost-effectiveness SLR. No further records were identified from other hand searching methods.

Therefore, a total of 13 publications were included in the cost-effectiveness SLR from the database searches, grey literature searches, and hand searching. The flow of studies through the review is reported in the PRISMA flow diagram in Figure 62.

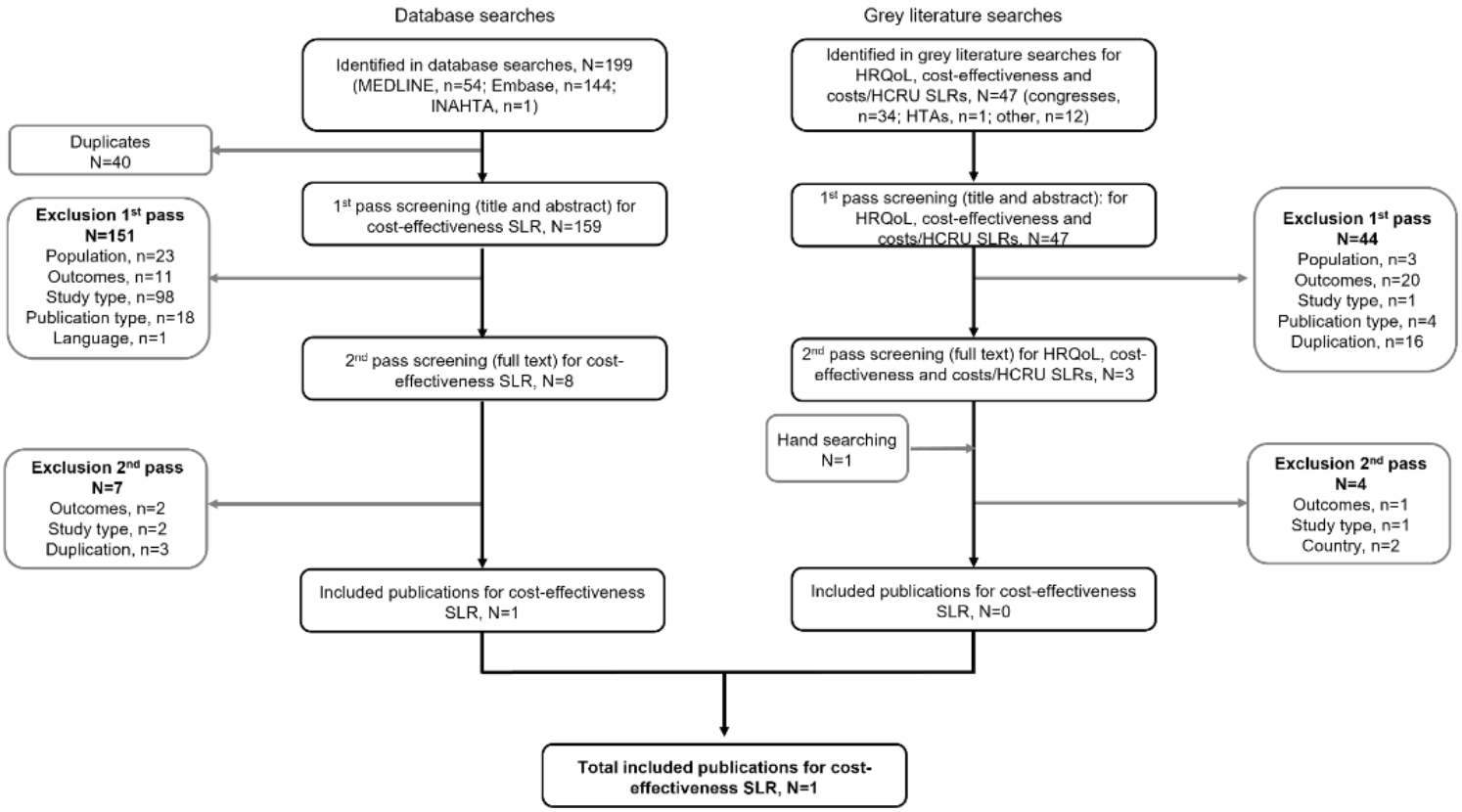
An update of the SLR was run for the period 07 May 2024 to 08 November 2024. One new publication was identified. The flow of studies through the review is reported in the PRISMA flow diagram in Figure 63

Figure 62: PRISMA flow diagram for the original cost-effectiveness SLR


Database searches
Grey literature searches
Identified in database searches, N=2,502 (MEDLINE, n=815; Embase, n=1,641; NHS EED/DARE, n=31; INAHTA, n=15)
Identified in grey literature searches for HRQoL, cost-effectiveness and costs/HCRU SLRs, N=388 (congresses, n=250; HTAs, n=39; other, n=99)
Duplicates N=552
1st pass screening (title and abstract) for cost-effectiveness SLR, N=1,950
1st pass screening (title and abstract) for HRQoL, cost-effectiveness and costs/HCRU SLRs, N=388
Exclusion 1st pass N=1,871
Population, n=198
Outcomes, n=393
Study type, n=515
Publication type, n=133
Publication year, n=473
Language, n=5
Duplication, n=136
SLR/NMA, n=18
Exclusion 1st pass N=370
Population, n=126
Outcomes, n=96
Study type, n=43
Publication type, n=43
County, n=4
Duplication, n=54
SLR/NMA, n=4
2nd pass screening (full text) for cost-effectiveness SLR, N=79
2nd pass screening (full text) for HRQoL, cost-effectiveness and costs/HCRU SLRs, N=18
Hand searching N=7
Exclusion 2nd pass N=68
Outcomes, n=35
Study type, n=27
Publication type, n=4
Publication year, n=2
Exclusion 2nd pass N=23
Population, n=1
Outcomes, n=10
Study type, n=1
Publication type, n=5
Country, n=5
Duplication, n=1
Included publications for cost-effectiveness SLR, N=11
Included publications for cost-effectiveness SLR, N=2
Total included publications for cost-effectiveness SLR, N=13

Abbreviations: DARE, Database of Abstracts of Reviews of Effects; HCRU, healthcare resource use; HRQoL, health-related quality of life; HTA, health technology assessment; INAHTA; International Health Technology Assessment Database; NHS EED, National Institute for Health Research Economic Evaluation Database; NMA, network meta-analysis; PRISMA, preferred reporting items for systematic reviews and meta-analyses; SLR, systematic literature review

Figure 63: PRISMA flow diagram for the cost-effectiveness SLR update



Abbreviations: HCRU, healthcare resource use; HRQoL, health-related quality of life; HTA, health technology assessment; INAHTA; International Health Technology Assessment Database; PRISMA, preferred reporting items for systematic reviews and meta-analyses; SLR, systematic literature review

Complete reference lists for included and excluded publications

Included studies

As per eligibility criteria, 14 relevant publications were identified. The full list of the identified publications is presented in Table 130.

Table 130: List of studies included in the cost-effectiveness SLR

Author(s)	Year	Title
J. Broomfield; M. Hill; F. Chandler; et al.	2024	Developing a Natural History Model for Duchenne muscular dystrophy
Z. Shehata; A. Metry; H. Rabea; et al.	2023	Early Cost-Utility Analysis of Ataluren and Eteplirsen in the Treatment of Duchenne muscular dystrophy in Egypt
A. C. Klimchak; L. E. Sedita; L. R. Rodino-Klapac; et al.	2023	Assessing the value of delandistrogene moxeparvovec (SRP-9001) gene therapy in patients with Duchenne muscular dystrophy in the United States
A. C. Klimchak; L. Sedita; K. L. Gooch; et al.	2023	EE291 Ethical Implications of Quality-Adjusted Life Year Assessments for Patients with Disabilities: A Duchenne muscular dystrophy Case Study
B. Innis; A. Henry; A. C. Klimchak; et al.	2023	EE392 The Potential Impact of Delandistrogene Moxeparvovec on Work Productivity on Individuals with Duchenne muscular dystrophy in the United States (US)
B. Innis; A. Henry; M. Zein; et al.	2023	EE401 Characterizing the Impact on Work Productivity in Patients with Duchenne muscular dystrophy and Caregivers: An Economic Analysis
J. Broomfield; M. Crowther; S. Freeman; et al.	2023	MSR147 Accounting for Study Heterogeneity When Modelling the Multi-State Natural History of Rare Diseases
NICE HST22	2023	Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene
D. Mujwara; R. McGonigal; J. Ford; et al.	2022	EE523 Assessing the Economic and Quality of Life Impact of Treatment in Duchenne muscular dystrophy
SMC2327	2021	ataluren (Translarna)

F. Agboola; G. A. Lin; N. Fluetsch; et al.	2020	The Effectiveness and Value of Deflazacort and Exon-Skipping Therapies for the Management of Duchenne muscular dystrophy
D. A. Magnetta; J. Kang; P. D. Wearden; et al.	2018	Cost-Effectiveness of Ventricular Assist Device Destination Therapy for Advanced Heart Failure in Duchenne muscular dystrophy
E. Landfeldt; L. Alfredsson; V. Straub; et al.	2017	Economic Evaluation in Duchenne muscular dystrophy: Model Frameworks for Cost-Effectiveness Analysis
Update review (November 2024)		
A. C. Klimchak; L.E. Sedita; E. M. Perfetto; et al.	2024	Discriminatory Properties of Quality-Adjusted Life Year Based Cost-Effectiveness Analyses for Patients With Disabilities: A Duchenne Muscular Dystrophy Case Study

Abbreviations: HST, Highly specialised technology; NICE, National Institute for Health and Care Excellence; SMC, Scottish Medicines Consortium; US, United States.

Excluded studies

Overall, 2,331 papers were excluded during first-pass and full-text screening in the original cost-effectiveness SLR. Through database searches, 1,871 papers were excluded during first-pass screening and 68 were excluded during full-text screening. Through grey literature searches, 370 publications were excluded during first-pass screening and 23 were excluded during full-text screening.

For the SLR update, a total of 206, publications were excluded; for the database searches 151 were excluded during first-pass screening and 7 during second-pass screening and for the grey literature searches 44 were excluded during first-pass screening and 4 during second-pass screening.

Due to the large number of excluded studies, these are attached as separate files (Italfarmaco 2024o, Italfarmaco 2024p, Italfarmaco 2024q, Italfarmaco 2024r, Italfarmaco 2024m, Italfarmaco 2024n).

Outcomes of included publications

Details regarding the 14 cost-effectiveness publications identified in the SLR are summarised in Table 131.

Table 131: Summary of results of the included cost-effectiveness studies

Author, year and Study details (e.g. patient population, model type and structure; time horizon; perspective; analyses; health states)	QALYs / DALYs/ LYGs (base case)		Total costs (base case)		ICER per QALY gained (base case)
	Intervention	Comparator	Intervention	Comparator	
Broomfield, 2024 **Initial pilot, in which information was elicited from four clinicians and four caregivers involved in the Project HERCULES collaboration.** **This was followed by an online survey of Duchenne UK stakeholders, with 20 responses from DMD parents, caregivers and practitioners (separate to the 20 UK-based clinicians who validated the final set of health states).** **Model and Health states:** **Ambulatory: EA/LA** **Transfer** **Non ambulatory: Hand-to-mouth function/ no ventilation to:** **No HTMF/No vent–No HTMF/night-time vent–Full-time ventilation**	It was estimated that, on average, patients spent approximately 9.5 years in the ambulatory states, 1.5 years in the transfer state and the remainder of their lives in the non-ambulatory states. Predicted median survival was 34.8 years.		NR	NR	NR

HTMF/night-time vent–No HTMF/night-time vent–Full-time ventilation **Death** **Lifetime time horizon** **Perspective NR** **To explore areas of uncertainty, a set of scenario analyses were performed. The NHM was generated with the transfer state (NHM A) and without (NHM B) in a scenario analysis to assess uncertainty associated with transitions into and out of the newly identified transfer state, where data were informed by the elicitation exercise.**			
Shehata, 2023 **79 caregivers of 97 patients with DMD**	NR	Total per patient direct annual costs of DMD in USD 2021: mean, $14,214; SD, $6,691; median, $12 886 Total per patient indirect annual costs of DMD in USD 2021: mean, $17,485; $9,240; median, $15,222	NR
Klimchack, 2023 • **Simulated cohort of 4-year-olds with DMD** • **Cost-effectiveness analysis using a five-state transition model**	Delandistrogene moxeparvovec resulted in 7.31 discounted projected QALYs gained vs. SOC (corticosteroids [prednisone/prednisolone], physical/occupational therapy, multidisciplinary assessments, and	Total discounted lifetime direct medical costs (non-treatment): Delandistrogene moxeparvovec $1,164,783	

• **Health states: (1) EA; (2) LA; (3) ENA; (4) LNA; (5) Death (DMD-related/all-cause)** • **Lifetime time horizon** • **US healthcare system perspective**	gastrointestinal/respiratory/cardiac management).	SOC $1,105,932	
Klimchack, 2023 (EE291) **ENA patients with DMD; Base case assessed a 13-year-old, Stage 4, ENA with DMD** **Analysis 1: Institute for Clinical and Economic Review's 2019 DMD model** **Analysis 2: ICER 5 health state DMD model was replicated and adapted for patients with DMD starting in different health states and ages; health states:** **Stage 1: presymptomatic** **Stage 2: EA** **Stage 3: LA** **Stage 4: ENA** **Stage 5: LNA** **Death**	At ≤$100,000/QALY: net incremental non-treatment costs exceeded the value treatment benefits (QALYs gained), implying no cost-effectiveness of any treatment, irrespective of the amount of benefit, even at a $0 treatment cost. At $150,000/QALY, annual maximum treatment costs ranged from$260–$430, which is less than the annual maximum treatment cost of generic prednisone ($550) QALY's gained: 10-year pause: 1.32 20-year pause: 2.30 40-year pause: 3.57	Analysis 1 NR Analysis 2: Annual direct medical costs: Stage 4: $33,096 Stage 5: $44,326 Incremental direct medical costs | base case 10-year pause: $193,300 20-year pause: $337,100 40-year pause: $523,600	NR

Time horizon NR; Perspective NR **Assumptions regarding utilities (0.21 at baseline [ENA] progressing to 0.18 [LNA]), health-state transitions, costs, and treatment benefits (10-, 20-, and 40-year pause in disease progression) were replicated per the published ICER report. Analyses included maximum cost-effective treatment cost at willingness-to-pay thresholds of $50,000/QALY, $100,000/QALY, and $150,000/QALY. Results rounded to neared $100. A scenario analysis assessed the impact of removing disease-related direct medical costs if treatment is deemed not cost-effective at zero costs despite QALY gains**	At $50,000/QALY 10-year pause: Never CE 20-year pause: Never CE 40-year pause: Never CE At $100,000/QALY 10-year pause: Never CE 20-year pause: Never CE 40-year pause: Never CE At $150,000/QALY 10-year pause: $260 20-year pause: $360 40-year pause: $430				
Innis, 2023 (EE392) **Homogenous cohort of 4-year-old EA DMD patients**	NR	NR	Analysis 1:	Analysis 1:	NR

Five-state partitioned survival model **Lifetime horizon; perspective NR** **Analysis 1: Individuals entered the model and were assigned to a treatment arm at 4 years old. Workforce participation was modelled for each DMD stage (EA: 100%, LA: 80%, ENA: 20%, LNA: 0%). Income was modelled using age-based median US salaries and mortality-adjusted employment by age; a growth rate of 2.8%/year and discount rate of 3%/year were applied** **Analysis 2: Delandistrogene moxeparvovec was assumed to be administered with SoC treatment, and its impact was modelled to be lifetime in the base case. Scenario analyses undertaken examined the impact of non-lifetime durability modelled at 10, 20, and 30 years, after which SoC progression resumes** **Health states: (1) EA; (2) LA; (3) ENA; (4) NA; (5) Death**			Working years lost: 25.48 Analysis 2: Working years: 11.25 Loss vs. US male pop: 25.48 (69.4%) Income (undiscounted): $1,689,248 Loss vs. US male pop: $5,752,074 (77.3%) Income (discounted): $601,610 Loss vs. US male pop: $1,547,283 (72.0%)	Working years lost: 35.85 Analysis 2: Working years: 0.88 Loss vs. US male pop: 35.85 (97.6%) Income (undiscounted): $63,096 Loss vs. US male pop: $7,378,226 (99.2%) Income (discounted): $35,085 Loss vs. US male pop: $2,113,808 (98.4%)	
Innis, 2023 (EE401) **Patients with DMD and their caregivers** **Five-state partitioned survival model**	NR	NR	Reduced work years for patients with DMD vs. general population (0.86 vs. 35.78) with lifetime loss of income of $1.9 million	NR

Lifetime time horizon

Perspective NR

Work productivity of patients with DMD and their caregivers was calculated and compared with that of the US general population to estimate work years and lifetime income lost. Salaries were adjusted for annual salary growth by 2.72% and a discount rate of 3% per annum was applied to potential earnings.

Health states: (1) EA; (2) LA; (3) ENA; (4) LNA; (5) Death

Caregivers lost more than 4 work years with potential losses of $165,000

Working years:

0.86 for patients with DMD vs. 35.78 for US male pop

20.05 for caregivers vs. 24.42 for general US pop

Income (undiscounted):

$57,355 for pts with DMD vs. $6,469,403 for US male pop

$2,046,976 for caregivers vs. $2,325,372 for general US pop

Income (discounted):

$32,902 for pts with DMD vs. $1,943,462 for US male pop

$1,218,359 for caregivers vs. $1,383,924 for general US pop

Difference:

Working years: 34.93 (97.6%) for patients with DMD vs. US male pop

		4.37 (17.9%) for caregivers vs. general US pop Income (undiscounted): $6,412,047 (99.1%) for patients with DMD vs. US male pop $278,396 (12.0%) for caregivers vs. general US pop Income (discounted): $1,910,560 (98.3%) for pts with DMD vs. US male pop $165,565 (12.0%) for caregivers vs. general US pop	
Broomfield, 2023 **3,166 patients with DMD across 25 international studies** **Five-stage multi-state natural history model** **Analysis 1: Four different methods were applied to estimate disease progression within a model for DMD; one that did not account for study source and three that did. The model structure, costs and utilities were obtained from a published model. A hypothetical treatment cohort was simulated**	Analysis 1: NR Analysis 2: Difference in QALYs by method Assumption based: 0.772 No adjustment: 0.325 One-stage frailty: 0.307 Two-stage proportional: 0.304 Two-stage stratified: 0.324	Analysis 1: NR Analysis 2: Difference in costs by method Assumption based: £1,517,000 No adjustment: £1,520,000 One-stage frailty: £1,427,000 Two-stage proportional: £1,399,000 Two-stage stratified: £1,229,000	Analysis 1: The ICER from the model not accounting for study source was consistently lower (~£2.2 million per QALY) than from the models that did (~£2.4-2.5 million per QALY). Analysis 2:

consistent with an example of an existing treatment for DMD. **Analysis 2: Three methods for predicting disease progression rates/probabilities that account for the study heterogeneity in the data were compared to a method that simply grouped the data together with no adjustment and an assumption based method used by Landfeldt et al. These three methods were a one-stage frailty model; a two-stage model assuming proportional baseline hazards; and a two-stage model assuming stratified baselines.** **Annual transition probabilities were calculated from the five methods (conditional on zero frailty for the one-stage frailty model). Annual costs and utilities were obtained from the literature. A treatment cohort was simulated assuming a 25% reduction in the annual transition probabilities between transient states, with an annual cost of £100,000. Costs and QALYs were discounted at 3.5%. These (limited) assumptions were consistent with Landfeldt et al. Health states: (1) EA; (2) LA; (3) ENA; (4) LNA; (5) Death**					ICERs by method Assumption based: £1,964,000 No adjustment: £4,672,000 One-stage frailty: £4,648,000 Two-stage proportional: £4,605,000 Two-stage stratified: £3,798,000
HST22, NICE	NR	NR	NR	NR	<£100,000

Semi-Markov model, partitioned survival models in each health state (ambulatory, non-ambulatory; FVC above 50%, below 50% and below 30%) **6 health states which represented the progression of DMD from the ambulatory phase to the non-ambulatory phases and death**			
Mujwara, 2022 **US DMD patients from ages 5 to <18 years** **Cost (2020 USD) and QoL calculator for direct and indirect costs and QALYs in DMD** **13-year time horizon** **Societal perspective** **Two scenarios were compared: with and without a hypothetical treatment that delayed LOA by 4 years as the patient progresses through early and late ambulatory and non-ambulatory stages. Sensitivity analyses included the hypothetical treatment in the direct costs and varied the assumption that the hypothetical drug delayed disease progression** **The natural progression of DMD was divided into four disease stages based on ambulatory status and years spent in each stage: EA (3 years) = 17%; LA (4**	Without treatment: 5.88 QALYs With treatment: 7.98 QALYs Outcomes over 13 year period: Patients that delayed LOA by 4 years gained 2.1 QALYs in a period of 13 years compared to those that did not have any delay in LOA	Outcomes over 1 year period: Annual total costs increased as the disease progressed: Early or late ambulatory: $18,178 ENA: $244,959 LNA: $356,619 The larger proportion of total costs was attributed to direct costs in the early or late ambulatory stages (97%) and to indirect costs in the early (67%) and late (69%) non-ambulatory disease stages Outcomes over 13 year period: Without treatment, total direct ($664,660) and indirect costs ($1,155,662) amounted to more than $1.82 million in 13years EA (3%)	NR

years) = 39%; ENA (4 years) = 17%; LNA (2 years) = 27%			LA (4%) ENA (54%) LNA (39%) Costs attributed to the patient's and caregiver's reduced quality of life had the largest impact on savings With treatment, total direct ($356,072) and indirect costs ($333,807) amounted to more than $689,878 in 13years		
SMC2327 **Patients aged ≥2 years old with DMD resulting from a nonsense mutation** **Cost-utility model** **Lifetime horizon** **NHS Scotland and social care, with the addition of caregiver QALYs. A wider societal perspective incorporating indirect costs was included among scenario analyses, which also addressed informal care costs** **Sensitivity and scenario analyses**	QALYs: 47.17 LYs: 21.90	QALYs: 38.55 LYs: 20.53	£5,200,244	£693,797	£522,664

A partitioned survival approach was adopted, with several health states. Patients entered the model in an ambulatory state. Subsequent states were loss of ambulation (fully wheelchair bound), predicted FVC greater or less than 50%, FVC <1 litre (FVC<1L), and death					
Agboola, 2020 **Hypothetical cohort of patients with DMD who began treatment at the age of 5 years** **De novo 5-state partitioned survival model** **Lifetime horizon** **Health care sector perspective and a societal perspective** **The 5 health states in the model were EA, LA, ENA, LNA, and death.**	Deflazacort vs. prednisone: Healthcare and societal perspectives: QALY: 8.40 LYs: 16.64	Deflazacort vs. prednisone: Healthcare and societal perspectives: QALY: 6.88 LYs: 15.05	Deflazacort vs. prednisone: net annual price: $81,400 Eteplirsen and golodirsen vs. SoC: $1,002,000	NR	Deflazacort vs. prednisone: Healthcare perspective: $344,000 Societal perspective: $371,000 Eteplirsen and golodirsen vs. SoC: $1,110,000
Magnetta, 2018 **Hypothetical cohort of patients with DMD and advanced heart failure** **Markov-state transition model** **5-year time horizon**	QALY: 1.99 LYGs: 3.13	QALY: 0.26 LYGs: 0.6	$435,602	$125,696	$179,086

	Healthcare sector perspective **Health states:** **DT-VAD: Death at implant; Implant survival-VAD replacement, Other readmission, Alive (no readmission), Death post DT-VAD** **Medical management: Readmission, Alive (no readmission), Death post-medical management** **Base case and multiple sensitivity analyses to account for potential uncertainties in our base-case assumptions and to explore circumstances under which each treatment strategy might be cost-effective at the $100,000/QALY willingness-to-pay threshold.**					
Landfeldt, 2017 **Patients with DMD aged ≥5** **Markov transition model, developed in Microsoft Excel®** **From the age of 5 years until death (or an age of 100 years)**	**Health states:** **Model I: total of 25 states, one for each DMDSAT score and an absorbing state for dead** **Model II: 5 states: (1) EA (approximately age 5–7 years); (2) LA (approximately age 8–11 years); (3) ENA (approximately age 12–15**	QALYs: Model I: Patient: 8.13 Caregiver: 12.93 Model II: Patient: 7.96	QALYs: Model I: Patient: 7.07 Caregiver: 12.80 Model II: Patient: 7.17	Costs: 2015 GBP (£) Healthcare perspective: Model I: 1,737,960 Model II: 1,768,370 Model III: 1,809,160 Societal perspective:	Costs: 2015 GBP (£) Healthcare perspective: Model I: 217,510 Model II: 244,120 Model III: 284,640 Societal perspective:	GBP (£) Healthcare perspective: Model I: 1,442,710 Model II: 1,939,590 Model III: 3,574,770 Societal perspective:

Base case: healthcare perspective **Scenario analysis: societal perspective** **Lifelong hypothetical intervention that reduced the probability of disease progression across all model states by a conservative (but realistic) 25%, in agreement with (but in addition to) the efficacy of glucocorticoid treatment observed in clinical practice**	**years); (4) ENA (approximately age 16 years or older); and (5) an absorbing state for dead** **Model III: 4 states: (1) no ventilation support; (2) night-time ventilation support; (3) day- and night-time ventilation support; and (4) an absorbing state for dead** **In each model, every cycle, patients had a probability of remaining in the current state, progressing to a more severe state, or dying**	Caregiver: 12.89 Model III: Patient: 6.39 Caregiver: 12.72	Caregiver : 12.82 Model III: Patient: 5.96; Caregiver: 12.66	Model I: 2,117,140 Model II: 2,171,380 Model III: 2,232,890	Model I: 624,240 Model II: 663,500 Model III: 713,840	Model I: 1,266,510 Model II: 1,760,650 Model III: 3,121,890
Klimchak, 2024 **Examined impact of QALY-based assessment on price for hypothetical treatment for DMD** **SoC as comparator: corticosteroids (prednisone) and medical management**		Early ambulatory population 10-year pause in progression: 4.62 QALYs gained vs SoC 20-year pause: 8.06 40-year pause: 12.53 Indefinite pause: 14.50		Early ambulatory population 10-year pause in progression: $81,317 incremental direct medical costs vs SoC 20-year pause: $141,816 40-year pause: $220,215 Indefinite pause: $204,803		Maximum annual treatment prices are reported for each WTP threshold. WTP $50,000/QALY Early ambulatory patients with 10-

Two patient populations assessed: (1) 5-year-old early ambulatory patients and (2) 13-year-old early non-ambulatory patients **5-state partitioned survival model** **Health states: early ambulatory, late ambulatory, early non-ambulatory, late non-ambulatory, dead** **Lifetime horizon** **US healthcare payer perspective** **Base case analyses: maximum annual treatment prices calculated for each population using WTP thresholds of $50,000/QALY, $100,000/QALY, $150,000/QALY, $200,000/QALY** **Three scenario analyses: maximum annual treatment prices calculated based on the evLYG, with utility values of 0.851 or 1.0 for extended survival; direct medical costs removed in any scenario that was not cost-effective at price of $0**	Early-non-ambulatory population 10-year pause in progression: 1.32 QALYs gained vs SoC 20-year pause: 2.30 40-year pause: 3.57 Indefinite pause: 3.86	Early non-ambulatory population 10-year pause in progression: $193,301 incremental direct medical costs vs SoC 20-year pause: $337,124 40-year pause: $523,625 Indefinite pause: $548,346	year, 20-year, 40-year, and indefinite pause in progression, respectively: $7,437, $10,992, $14,259, $17,666 Early non-ambulatory patients: no positive treatment price at which the hypothetical treatment would be cost-effective Further analyses were conducted at $100,000, $150,000 and $200,000 WTP thresholds

Abbreviations: CE, cost-effectiveness; DALY, disability-adjusted life years; DMD, Duchenne muscular dystrophy; DMDSAT, Duchenne muscular dystrophy Functional Ability Self-Assessment Tool; DT, destination therapy; EA, early ambulatory; ENA, early non-ambulatory; evLYG, equal value of life years gained; FVC, forced vital capacity; GBP, Great British Pounds; HST, highly specialised technology; HTMF, hand-to-mouth function; ICER, incremental cost-effectiveness ratio; LA, late ambulatory; LNA, late non-ambulatory; LOA, loss of ambulation; LY, life year; LYG, life years gained; NHM, natural history model; NHS, National Health Service; NICE, Nationale Institute for Health and Care Excellence; NR, not reported; pop; population; QALY, quality-adjusted life year; QoL, quality of life; SMC, Scottish Medicines Consortium; SoC, standard of care; UK, United Kingdom; USD, United States dollar; US, United States; VAD, ventricular assist device; WTP, willingness-to-pay.

Critical appraisal for each study

Critical appraisal of the identified economic evaluation studies was conducted using the Drummond checklist. Otherwise, studies were checked for compliance with the NICE reference case by two independent reviewers (Appendix K). The quality assessment of the included studies in the cost-effectiveness, HRQoL (Appendix I), and costs and resource use (Appendix J) SLRs are attached as a separate file: Utilities Cost Economic database screening_240513/241113, Utilities Cost Economic FTR screening_240606/241121 and Grey literature screening_clinical and costs/_241111

Appendix L. Duchenne Muscular Dystrophy

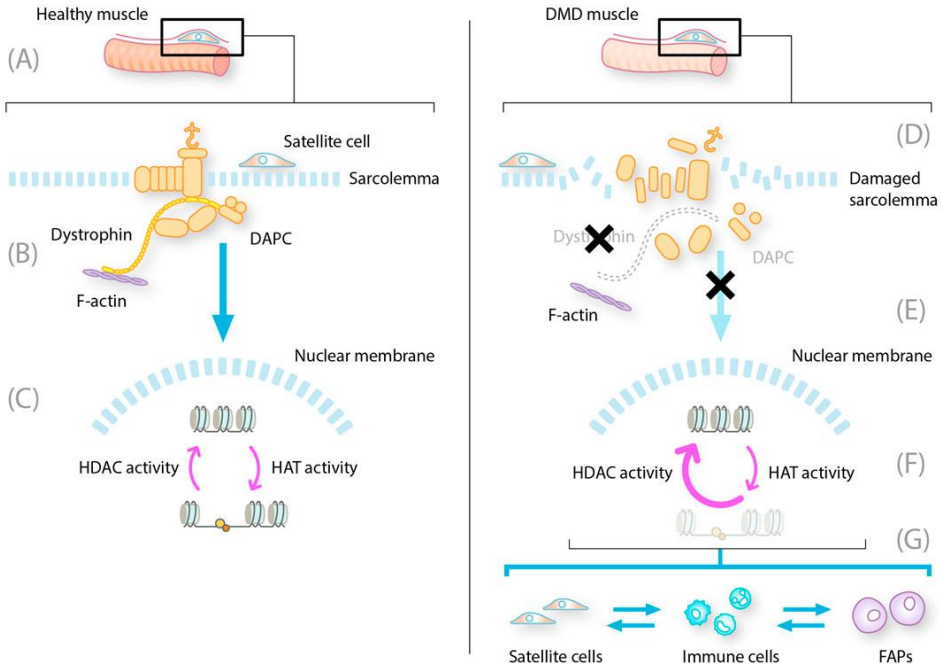
Disease aetiology

Duchenne Muscular Dystrophy (DMD) is a rare, irreversible, rapidly progressing, lethal neuromuscular disorder, almost exclusively affecting males due to its X-linked recessive genetic pattern (Ryder et al. 2017). DMD results from mutations in the DMD gene encoding dystrophin, the largest known human gene (Aartsma-Rus et al. 2016, Okubo et al. 2017). These mutations result in the absence of functional dystrophin (Blake et al. 2002, Hoffman et al. 1987).

Disease pathophysiology

Dystrophin is a key protein in the dystrophin-associated protein complex (DAPC). Without dystrophin, DAPC disassembles, compromising sarcolemma integrity and making muscle fibers susceptible to contraction-induced damage, progressive muscle wasting (Aartsma-Rus, 2025). Furthermore, lack of dystrophin halts the body's ability to repair and to regenerate new muscle cells. Lack of dystrophin leads to HDAC hyperactivation, a core element of the DMD pathophysiology, resulting in epigenetic changes causing inhibition of muscle regeneration factors, chronic inflammation, and replacement of muscle tissue with fibrotic and fat tissue (Figure 64) (Aartsma-Rus 2025, Bez Batti Angulski et al. 2023, Giordano et al. 2015).

Figure 64: Constitutive HDAC activity contributes to dystrophic muscle pathology



Notes: LEFT: healthy muscle fibers with intact DAPC. (A) MuSC and satellite cells reside on the muscle fibers ready to differentiate into new muscle(B) DAPC regulates activity of HDAC to allow translation of muscle

regeneration factors (C) In the nucleus HDAC and HAT work in balance to regulate the expression of muscle regeneration factors (MRF) RIGHT: DMD muscle with mutated dystrophin and disrupted DAPC (D) Absent dystrophin leads to disruption of the DAPC with multiple consequences for muscle repair (E) These consequences include damage to the sarcolemma leading to cytoplasmic leakage displacement of NOS and decreased levels of NO, which, in turn, lead to aberrant constitutive expression of HDACs (F) Increased HDAC activity results in repression of translation and transcription of muscle repair an MRF (G) The absence of gene transcription leads to changes in the production of new myofibres from satellite cells, prolongation of inflammatory phases of repair into a chronic state, and induction of FAP differentiation into fibroblasts and adipocytes.

Abbreviations: DAPC, dystrophin-associated protein complex; FAP, fibro-adipogenic progenitor; HAT, histone acetyltransferase; HDAC, histone deacetylase; MuSC, muscle stem cell; NO, nitrous oxide; NOS, nitric oxide synthase.

Reference: Aartsma-Rus (2025)

In DMD, both innate and adaptive immune pathways remain chronically activated compared to healthy muscle tissue, suppressing muscle regenerative capacity even in areas where necrotic debris has been cleared. Fibro-adipogenic progenitors (FAPs) become persistently active, driving fibrosis and fat infiltration, while muscle stem cells (MuSCs) undergo maladaptive differentiation into FAPs rather than replenishing muscle fibers (Giuliani et al. 2022). This imbalance reduces the myogenic progenitor pool, reinforcing progressive muscle loss and functional decline, hallmarking DMD as a severe, degenerative muscle-wasting disease (Kodippili and Rudnicki 2023).

Role of HDAC hyperactivation in DMD pathophysiology

A lack of dystrophin leads to the aberrant hyperactivation of histone deacetylases (HDACs), which plays a pivotal role in disease progression (Mozzetta et al. 2024, Rugowska et al. 2021). Dystrophin, as part of the DAPC, normally anchors nitric oxide synthase (NOS) to the sarcolemma, regulating HDAC activity through NO-mediated S-nitrosylation. In DMD, DAPC dissembling leads to NOS mislocalization resulting in sustained HDAC hyperactivity, suppressing key myogenic genes, impairing muscle regeneration, and exacerbating chronic inflammation and fibro-adipogenic remodeling (Saccone et al. 2014, Marrone and Shcherbata 2011).

HDAC hyperactivation has many pathological consequences:

1. Epigenetic Dysregulation – HDACs excessively deacetylate histones, compacting chromatin and repressing key myogenic genes, impairing satellite cell differentiation and muscle regeneration (Saccone et al. 2014, Rugowska et al. 2021).

2. Chronic Inflammation – HDACs alter immune cell balance, promoting sustained pro-inflammatory signaling and muscle infiltration by immune cells, exacerbating tissue damage (Bez Batti Angulski et al. 2023, Licciardi and Karagiannis 2012).

3. Fibro-Adipogenic Remodeling – HDAC hyperactivity disrupts fibro-adipogenic progenitor (FAP) regulation, preventing their transition into a pro-regenerative state and instead promoting excessive fibrosis and fat deposition (Ren et al. 2024, Sandonà et al. 2016).

4. TGF-β Signaling Modulation – HDACs regulate SMAD acetylation, influencing TGF-β pathways, which further drive fibrotic remodeling and loss of muscle function (Osseni et al. 2022, Molinari et al. 2023).

Targeting HDAC activity through pharmacological inhibition has been shown to counteract these pathological mechanisms by restoring muscle homeostasis, reducing fibrosis and

inflammation, and slowing disease progression in preclinical and clinical DMD studies (Mozzetta et al. 2024, Mercuri et al. 2024b, Lamb 2024). Given that DMD involves irreversible muscle degeneration, early therapeutic intervention is crucial to maximizing functional preservation and delaying key disease milestones (Molinari et al. 2023).

Diagnosis

Ensuring a timely and accurate diagnosis of DMD is crucial for effective management, allowing early intervention and appropriate genetic counselling. A dystrophinopathy should be suspected in patients with symptoms of weakness, characteristic physical exam, and a possible family history of the disease (Zambon et al. 2022). Laboratory testing involves creatinine kinase measurements, muscle biopsies, gene testing, and electrocardiogram (ECG) findings for cardiomyopathy. Diagnosis should be conducted by a neuromuscular specialist who can clinically evaluate the patient and efficiently obtain and interpret the diagnostic tests in the context of the clinical presentation (Birnkrant et al. 2018a, Aartsma-Rus et al. 2019). Following a DMD diagnosis, carrier testing and genetic counselling are essential (Birnkrant et al. 2018a).

Apart from routine diagnostics for confirmation of DMD diagnosis, there is no additional diagnostic tests needed to be eligible for givinostat (European Medicines Agency 2025).

DMD Disease Course

DMD is characterised by early progressive and irreversible muscle degeneration injury of all muscles throughout the body, ultimately resulting in the loss of ambulation and wheelchair dependency, then continuing with disease progression to result in upper limb dysfunction, respiratory failure, cardiomyopathy and a premature death (Figure 2) (Duan et al. 2021, Walter and Reilich 2017, Andreozzi et al. 2022). The disease follows a predictable but heterogeneous trajectory, with considerable variability in disease severity and progression rates among patients (Ciafaloni et al. 2016). However, in all cases, DMD is linked to severe outcomes and reduced life expectancy. The median life expectancy of 22–28 years (Italfarmaco UK 2024, Broomfield et al. 2023, Broomfield et al. 2021, Nart et al. 2024, Pietrusz et al. 2023) which is similar to the mean age of death in Denmark (26.8 years) (Rudolfsen et al. 2024).

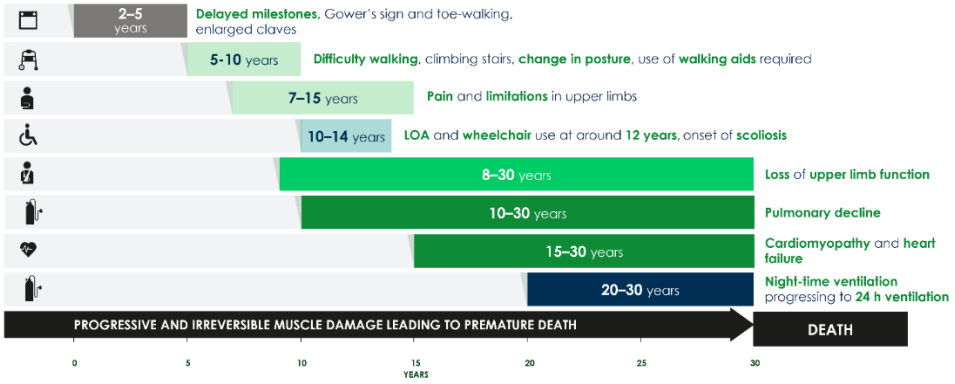
While concurrent, progressive muscle injury of all muscles starts at birth, during the natural course of the disease, impairment of lower limb function is typically observed first and as patients age, muscular damage accumulates, leading to increasing symptom severity and lowered function scores (Walter and Reilich 2017, Andreozzi et al. 2022). Initially, boys and young men with DMD experience sequential loss of important early developmental milestones, including difficulties getting up from the floor, standing, walking, and climbing stairs (Andreozzi et al. 2022, McDonald et al. 2022b). These difficulties contribute to frequent falls and a considerable risk of bone fractures (Birnkrant et al. 2018a, Ryder et al. 2017, Ciafaloni et al. 2016, Houwen-van Opstal et al. 2021). The decline in lower limb function becomes apparent in the initial decade of life, ultimately leading to loss of ambulation (LoA) and wheelchair dependency in the early teens (McDonald et al. 2017, Annexstad et al. 2019).

Around the time of LoA, upper limb function also starts to deteriorate, with loss of shoulder elevation and hand-to-mouth activity occurring from the mid-teens (Walter and Reilich 2017). As a consequence of increasing upper limb muscle weakness, boys and young men with DMD experience a deterioration in their hand skills, which follows from decreased joint mobility and contractures in the wrist and fingers (Eriksson et al. 2024). This prevents them from using, for example, computers and smartphones, that would otherwise provide virtual access to their friends, hobbies and interests and overcome any social isolation resulting from their physical disability.

Alongside this, continued muscle weakening, particularly of the intercostal muscles and diaphragm, increases the need for cough and ventilatory support (Andreozzi et al. 2022, McDonald et al. 2022b)**,** partial and then full-time ventilation assistance and possibly tracheostomy (Andrews and Wahl 2018). DMD is also associated with dilated cardiomyopathy that contributes to heart failure and arrhythmias (Schultz et al. 2022) leading to premature death (Walter and Reilich 2017)**.** Clinically apparent cardiomyopathy is first evident after 10 years of age and increases in incidence with age, being present in all patients over 18 years of age (Nigro et al. 1990). Cardiovascular and respiratory complications are the leading causes of morbidity, unplanned hospital admissions and mortality in boys and young men with DMD (Birnkrant et al. 2018c, Childs et al. 2024).

Although DMD has principally been studied in the context of skeletal muscle dysfunction, it is a multisystem disorder because dystrophin is also expressed in cardiac and smooth muscle, endocrine glands, and neurons (Rae and O'Malley 2016). Consistent with dystrophin's functional importance in the central nervous system, boys and young men with DMD often exhibit varying degrees of non-progressing cognitive impairment, with their intelligence quotients (IQ) shifted downward one standard deviation below the normal range (Anderson et al. 2002, Bresolin et al. 1994, Felisari et al. 2000). A well-recognized pattern of cognitive strengths and weaknesses can be observed in the neuropsychological profiles of DMD patients, which might warrant diagnosis of a comorbid neurodevelopmental or neuropsychiatric disorder (Birnkrant et al. 2018d).

Figure 2: Consequences of DMD disease progression



Abbreviations: DMD, Duchenne muscular dystrophy; LoA, loss of ambulation.

Adapted from: 1. Birnkrant et al. (2018a); 2. Nowak and Davies (2004); 3. Duan et al. (2021); 4. Duchenne UK (2025a); 5. Archer et al. (2016); 6. Rall and Grimm (2012); 7. Koeks et al. (2017); 8. Ryder et al. (2017); 9. Birnkrant et al. (2018c); 10. LoMauro et al. (2015); 11. Emery (2002); 12. Passamano et al. (2012).

Staging/classification of DMD

DMD can be classified into five stages according to the appearance and progression of symptoms: Stage 1 or pre-symptomatic, Stage 2 or early ambulatory, Stage 3 or late ambulatory, Stage 4 or early non-ambulatory, and Stage 5 or late non-ambulatory (Birnkrant et al. 2018d) (Table 132).

Table 132: DMD disease symptoms and milestones

Disease Stage	Age	Identifying Symptoms and Disease Milestone
Pre-symptomatic	1 to 3 years old	• First symptoms of development delay, including delayed walking, frequent falls, and difficulty with running and climbing stairs • Bulky calf, pelvis, and thigh muscles • Gait disturbance not yet apparent
Early Ambulatory	4 to 7 years old	• Gower's sign, waddling gait, toe walking • Ability to climb stairs is retained
Late Ambulatory	8 to 11 years old	• Progressively laboured gait and decreased walking ability • Loss of ability to climb stairs and rise from the floor • Patients may use a wheelchair part-time
Early Non-Ambulatory	12 to 19 years old	• Transition to a wheelchair-bound state, ability to self-propel and maintain posture is retained for a period • Development of scoliosis and muscular contractures • Increased risk of respiratory complications and onset of cardiomyopathy • May require night-time ventilation
Late Non-Ambulatory	>19 years old	• Pronounced limitations • Increasingly limited upper limb function and postural maintenance • Increased cardiomyopathies • Loss of hand-to-mouth function • Requires night-time ventilation or full ventilation

Abbreviations: DMD: Duchenne muscular dystrophy
References: Bello et al. (2016), Bushby et al. (2010), Ryder et al. (2017)

Complications

DMD complications include orthopaedic, respiratory and cardiac complications.

Orthopaedic complications

Once children lose ambulation, care is taken to closely monitor their spines and heart. The spine develops scoliosis i.e. curvature of the spine, which needs its own management and may require scoliosis surgery. As scoliosis progresses, it may have a significant impact on the respiratory system and affect positioning and comfort in a wheelchair (Koumbourlis 2006). As a result, most patients with scoliosis undergo spinal fusion surgery (Cheuk et al. 2007). Rudolfsen et al. found that for DMD patients in Denmark above 12 years of age 39% had a diagnosis of scoliosis (Rudolfsen et al. 2024). DMD patients have a lower bone and muscle mass, a higher fraction of fat mass versus muscle, and a higher likelihood of experiencing fractures due to fragility compared with patients without the condition. This can be attributed to limited mobility, loss of muscle

mass, and the prolonged use of GCs (Apkon et al. 2018, Bell et al. 2017, Mayo et al. 2012).

Respiratory complications

Respiratory weakness in DMD is inevitable but usually becomes clinically relevant after loss of ambulation and strongly correlates with the progression of upper limb weakness (Childs et al. 2024). It typically begins to manifest during the later stages of the disease, often around the teenage years (12–18 years), and increases as the patients grow older (**Table** 133) (Delaney and O'Halloran 2024). The impact of DMD on respiratory function is largely a result of intercostal and diaphragm muscle weakness (Childs et al. 2024). Boys and young men with DMD experience respiratory muscle fatigue, which leads to a decline in vital capacity and the development of stiff, non-compliant chest walls and lung volume restriction (Birnkrant et al. 2018c). Mean annual decline for forced vital capacity (FVC) %-predicted was 5.6% (standard error: 2.1%) percentage points before loss of ambulation and 10.1% (2.2%) after loss of ambulation (McDonald et al. 2024). During the non-ambulatory stage, boys and young men with DMD develop weak cough efforts, placing them at risk of mucus plugging, atelectasis, pneumonia, ventilation-perfusion mismatch, and a heightened risk of progressing to respiratory failure, especially during respiratory tract infections (Birnkrant et al. 2018c).

In a Norwegian study, 17% of patients required treatment for left ventricular dysfunction, initiated at a mean age of 12.1 years (SD ± 3.0), while 12% required nighttime non-invasive positive pressure ventilation (NIPPV) from an average age of 13.0 years (SD ± 2.5) (Annexstad et al., 2019). Danish experts has validated this to be similar for Denmark (Italfarmaco 2024e, Italfarmaco 2024c).

Table 133: Needs of respiratory comorbidity management in each stage of DMD

Stage of the disease	Required pulmonary test
Ambulatory stage	• FVC monitoring and sleep studies
Early non-ambulatory stage	• Consistent pulmonary assessments • Scoliosis surgery in some cases • Assisted ventilation
Late non-ambulatory stage	• Assisted ventilation • Full ventilation

Abbreviations: DMD: Duchenne Muscular Dystrophy; FVC: forced vital capacity
References: Birnkrant et al. (2018c)

Ventilatory support is frequently required at this stage of the disease, initially overnight, but later, it may be needed 24 hours/day (Childs et al. 2024). Non-invasive ventilation is considered in the first instance, but tracheostomy may be required during periods of acute illness (Childs et al. 2024). Patients are at risk of severe dyspnoea, extended hospital admissions due to atelectasis or pneumonia, and fatal outcomes due to respiratory arrest or respiratory-induced cardiac arrhythmias (Birnkrant et al. 2018c). Maintaining respiratory health is vital to prolonging survival and QoL in DMD (Childs et al. 2024).

A Danish register study estimated the mean age at first respiratory mask treatment to 15.3 years (141 individuals), and in total identified 127 individuals with DMD being registered with in-home mechanical ventilation (Rudolfsen et al. 2024). In a Norwegian study of boys with DMD below 18 years of age, 19% had access to a coughing device, but only 11% used their device regularly. Night-time hypoventilation or obstructive sleep apnoea was diagnosed in eight of 65 boys (12%) under 18 years, the youngest of whom was 12.3 years at the time of study examination.

In the later stages of DMD, pharyngeal weakness leads to dysphagia, resulting in poor oral food intake. When combined with poor respiratory function, this can result in severe weight loss and the need to consider tube feeding (Birnkrant et al. 2018a).

Cardiac complications

The absence of dystrophin in the cardiomyocytes results in increased cardiomyocyte structural vulnerability, membrane instability, disruption in Ca^{2+} homeostasis, elevated production of reactive oxygen species ROS, and mitochondrial dysfunction. Furthermore, dystrophin is also expressed in endothelial cells, vascular smooth muscle cells, and fibroblasts. As a result, DMD patients experience cardiac complications, including diminished heart beating capacity, electrical conduction and electrocardiogram (ECG) abnormalities such as atrial and ventricular tachycardias, and atrial arrhythmias (Birnkrant et al. 2018c, Łoboda et al. 2020).

Most DMD patients develop symptoms of cardiomyopathy during their teenage years, (Birnkrant et al. 2018b) and nearly all DMD patients will eventually have developed dilated cardiomyopathy (Andrews and Wahl 2018), with a mean age of onset at approximately 15.26 years (Broomfield et al. 2023). As patients grow older, they experience increasing left ventricular (LV) dysfunction, dilation, and fibrosis. Ultimately, this trajectory leads to end-stage heart failure characterized by systolic dysfunction and dilated cardiomyopathy (Łoboda et al. 2020).

Mortality

Ventilatory support has improved DMD patients' life expectancy. A systematic review showed that the median survival age in DMD patients not receiving ventilatory support was between 14 and 27 years old, which increases with a ventilatory support, with a range between 21 and 39 years old (Landfeldt et al. 2020, Orso et al. 2023). In a recent report from the NMiS (Swedish National Registry for Neuromuscular Disorders) during 2025, the median survival age is [redacted] years and the mean [redacted] (Italfarmaco 2025b). In Danmark the median survival for DMD patients is 26.8 years (Rudolfsen et al. 2024). Mortality and DMD survival data has been extensively documented in several studies, indicating that the median survival age for boys and young men with DMD is 22–28 years (Broomfield et al. 2023, Broomfield et al. 2021, Nart et al. 2024, Pietrusz et al. 2023) and only very few patients survive beyond the third decade (Passamano et al. 2012, Emery 2002, Rall and Grimm 2012), which is consistent with data from the Nordic region (Italfarmaco 2024f).

Burden of disease in DMD

DMD is a severe, rapidly progressing rare, lethal neuromuscular muscle-wasting disease leading to progressive debilitation and irreversible loss of muscle, resulting into losing ambulatory capacity, respiratory and cardiac complications and a premature death. To the date, there is no cure.

The burden of DMD on patients and their families is profound. Physically, patients experience early loss of ambulation, often requiring wheelchairs by their early teens, followed by complications such as respiratory decline and cardiomyopathy, and premature death. Psychologically, the loss of independence and chronic health challenges weigh heavily on both patients and caregivers. The disease also imposes a significant economic burden due to healthcare costs, several assistive devices, and the need for long-term caregiving by both family and external help. Despite advances in care, DMD remains a life-limiting condition with devastating impacts on quality of life for both patient, carers and society.

Patient burden and impact on quality of life

Boys and young men with DMD and their families require support from a multidisciplinary team of experts in neurology, endocrinology, cardiac, emergency care, psychosocial, nutrition, orthopaedics, physiotherapy, and respiratory specialities (Italfarmaco 2024f, Italfarmaco 2024d, DMD Care UK 2024). As described in Appendix 0 above, DMD complications include orthopaedic complications, cardiac complications, and respiratory complications, in addition to progressive muscle weakness and loss of functions.

Losing lower limb function

Limited data describe the experiences of boys and young men with DMD, particularly during the non-ambulatory stage. However, a qualitative study of forty-six patient/caregiver dyads (pairs), including non-ambulatory patients, aimed to capture the lived experience of the disease (Brown et al. 2023)

Study participants described the most bothersome challenges of living with DMD as the mobility restrictions they experienced, as well as the emotional and social impacts that resulted from their physical function limitations. All ambulatory dyads (n=28, 100%) reported difficulties with weakness or lack of strength, and most reported tiring easily or lacking energy (n=24, 86%). Almost all ambulatory dyads reported at least one difficulty with mobility, including going up and down stairs (n=16, 57%), running (n=13, 46%), and walking (n=9, 32%). Approximately half of the ambulatory dyads reported the inability to keep up physically with their peers (n=15, 54%) and/or mobility restrictions (n = 14, 50%). These challenges impacted their ability to engage in activities they want to do, such as participation with their peers and negatively impacted their mood (Brown et al. 2023).

Similarly, among the non-ambulatory dyads, lack of mobility (n=10, 56%) and inability to keep up with peers (n=5, 28%) were reported to be the biggest challenges, which often

resulted in negative emotions and feeling different from peers and limited their ability to participate in social activities, play, and sports (Brown et al. 2023).

Losing upper limb function

The loss of upper limb function leads to severe problems in performing daily activities and participating in society, ultimately affecting independence and QoL (Janssen et al. 2016). While the use of a wheelchair could facilitate independence, loss of upper limb function is more often framed as a source of ongoing frustration due to a steady decline in the ability to carry out self-care and leisure activities independently (Bever et al. 2024). Adolescence is usually a time of growing independence and autonomy, but for boys and young men with DMD, their parents will need to provide increasing assistance with intimate and personal care (e.g. dressing, eating, washing and toileting) (Landfeldt et al. 2016b).

In the patient burden study, symptoms and impacts associated with impaired upper body function included difficulties with reaching for objects (n=14, 78%), fine motor skills such as holding a pencil or turning pages in a book (n=11, 61%), lifting arms above the head (n=10, 56%), and lifting objects (n=8, 44%), which resulted in patients needing additional assistance from caregivers or adaptive devices. Limitations in upper body function resulted in all non-ambulatory participants needing assistance with at least one ADL, including getting dressed (n=15, 83%), bathing (n=12, 67%), toileting (n=8, 44%), and eating and drinking (n=7, 39%). Most non-ambulatory participants reported needing help with transfers, such as getting in and out of bed (n=13, 72%), getting in and out of chairs (n=10, 56%), and being positioned when in bed (n=10, 56%), which further limited their independence. As a result of needing caregivers to reposition them during the night, most non-ambulatory dyads also described sleep problems and fatigue (both n=14, 78%).

Preserving upper limb function in boys and young men with DMD is therefore important as it relates to independence and HRQoL. Worsening upper limb function correlates with a decline in HRQoL, as measured by European Quality of Life 5 dimensions 5 level version (EQ-5D-5L) scores, in individuals with DMD aged 12–40 years (Audhya et al. 2023b).

Social limitations

Social closeness with peers with similar life experiences can enhance the physical and psychological well-being of young men with DMD (Accogli et al. 2022). In a qualitative study of the psychosocial impacts of living with DMD, it appeared that social inclusion was particularly lacking during the transition into adulthood. Some young men with DMD described a narrowing of social opportunities and insufficient social supports to meet their changing needs. Participants related how social opportunities were limited because friends establish working lifestyles in which they are unable to readily fit. While some degree of social engagement may be maintained through online connections like multiplayer video games, disease progression was associated with social isolation (Bever et al. 2024).

Transition between paediatric and adult services

As children with DMD can be diagnosed as early as two years of age and live until their mid-20s, there is a necessary transition of care from paediatric to adult services over the individuals' life course. However, because of their highly complex healthcare needs that require the coordinated support of many different specialists, this transition of care can be difficult and can occur in a piecemeal fashion for boys and young men with DMD and, therefore, must be planned carefully (Wasilewska et al. 2020).

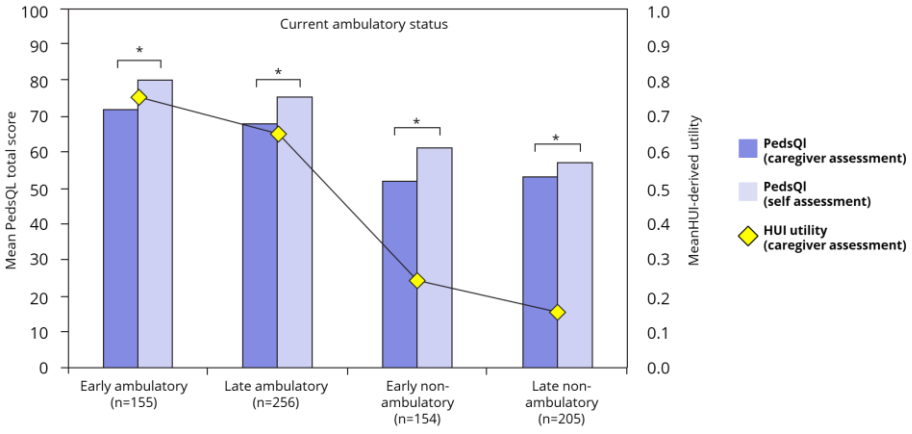
In Denmark the follow up treatment and caring after transition to adult services depends on the wishes of the patient and the treatment environment in the local area. It can differ depending on where the patient lives (Italfarmaco 2024e, Italfarmaco 2024c, Italfarmaco 2024d, Italfarmaco 2024f). This transition occurs when boys turn 18 years. Inadequately planned transition processes could lead to negative outcomes related to mortality, prognosis, psychosocial and educational well-being (Accogli et al. 2022, Wasilewska et al. 2020).

Overall impact on quality of life

Boys and young men with DMD experience significantly compromised HRQoL, which deteriorates with functional decline (Figure 65), and highlights the importance of delaying disease progression (Landfeldt et al. 2016a). Comparisons of QoL between boys and young men with DMD and the general population reveal substantial disparities, with boys and young men with DMD consistently reporting lower HRQoL scores across a range of HRQoL measures (Orso et al. 2023, Landfeldt et al. 2020).

Contributing factors to this decline in HRQoL include motor and respiratory dysfunctions, muscle weakness, pain, dependence on help with daily activities, and disruptions in sleep quality.

Figure 65: Self-assessed and caregiver proxy-assessed patient HRQoL by ambulatory status



Abbreviations: HUI: Health Utilities Index; PedsQL: Pediatric Quality of Life Inventory.
References: Landfeldt et al. (2016a)

Loss of ambulation is a key milestone in DMD disease progression, typically occurring at 11-12 years of age and significantly impacts patients' HRQoL (Andreozzi et al. 2022). When patients lose the ability to walk, their HRQoL declines (Figure 65, Table 134).

Table 134: Mean EQ-5D-5L scores in participants with DMD with declining limb function

Ambulation stage	Upper limb function	N	EQ-5D-5L, mean (SD)
Early ambulatory	Preserved	10	0.84 (0.13)
Late ambulatory	Preserved	6	0.59 (0.33)
Early non-ambulatory	Preserved	2	0.46 (0.10)
Early non-ambulatory	Mildly impaired	16	0.30 (0.14)
Late non-ambulatory	Moderately impaired	9	0.22 (0.15)
Late non-ambulatory	Lost	1	0.26 (N/A)

Abbreviations: DMD: Duchenne muscular dystrophy; EQ-5D-5L: European Quality of Life 5 dimensions 5 level version.
References: Audhya et al. (2023b)

Caregiver burden

Impact of DMD on children, caregivers, family members and the wider community
Caring for boys and young men with DMD is mentally and physically exhausting, time-consuming and complex, typically requiring multiple caregivers, alongside the multidisciplinary healthcare team. Care not only includes emotional and social support and assistance with basic and instrumental ADLs, but it also requires attendance at regular healthcare appointments and any additional visits mandated by clinical trial protocols and the associated travel, time to complete bureaucratic processes to obtain funding or various aspects of the child's care, and investment in home modifications to accommodate mobility aids and medical equipment (Duchenne UK 2024, Landfeldt et al. 2016b, Magliano et al. 2015).

The burden for caregivers increases with disease progression, significantly impacting caregivers' overall QoL, physical, emotional and mental well-being, and employment status (Landfeldt et al. 2016b, Porteous et al. 2021, Landfeldt et al. 2018, Pfizer UK 2024a). Moreover, the impact of DMD extends beyond the person with DMD and their parents to siblings, grandparents, the wider family, and the local community. The most significant changes in a child's physical ability occur during their school years. As well as the adaptations required at home, the presence of additional physical, behavioural, and learning needs requires local authority funding for specialist support and adaptations to the classroom environment to ensure children with DMD can reach their potential (FDA 2024, Muscular Dystrophy Assoc. 2024).

Caregiver physical status

Over 50% of the parents of boys and young men with DMD face health issues due to the burden of their child's disease, leading to need for medical treatment (Schreiber-Katz et al. 2014). In a cross-sectional study assessing all boys and young men with a confirmed diagnosis of DMD or Becker muscular dystrophy (n=733) and their caregivers via the German dystrophinopathy patient registry, it was observed that parents' health status

not only significantly affected their ability to provide care to their child but also impacted their work capacity, resulting in indirect costs (Schreiber-Katz et al. 2014). In another cross-sectional assessment of caregiver QoL and burden showed that caregivers of boys and young men with DMD are more likely to experience a higher prevalence of pain and discomfort compared with the reference data for the general population (44% vs. 33%, p<0.001) and problems performing usual activities (18% vs. 16%, p=0.006) (Landfeldt et al. 2016b, Landfeldt et al. 2018).

Emotional and mental status

Unlike caregivers of children without DMD, caregivers of boys and young men with DMD face additional constraints and hidden costs that impact their health and financial well-being, extending long beyond the usual period of childhood dependency. As a result, caregivers of boys and young men with DMD have reported worse mental health, difficulty paying bills, and more hours missed from work than parents without a child diagnosed with DMD (Schwartz et al. 2021). Caregivers of boys and young men with DMD are at a notable risk of experiencing anxiety, depression, and impaired mental health, as shown in a cross-sectional study where approximately 50% of caregivers reported being moderately or extremely anxious or depressed, significantly higher than the general population (p<0.001) (Landfeldt et al. 2016b, Landfeldt et al. 2018). Such anxiety and depression stems from the social limitations, and great time devoted to caring for a boys and young men with DMD (Balidemaj et al. 2023). Caregivers' anxiety and depression levels often peak with experiencing shock at diagnosis and with each milestone in the patient's disease progression, such as loss of ambulation, requirement for enteral feeding, and need for non-invasive ventilation (Donnelly et al. 2023, Porteous et al. 2021).

Although at its most intense at the time of death of their child, similar to their experience of anxiety and depression, parents' experience of grief arose before bereavement and reached heightened states at each disease progression point (Donnelly et al. 2023). The guilt experienced by carriers tends to relate to self-blame associated with the death of their son and may increase the risk of experiencing complex or prolonged grief after bereavement (Duffy and Wild 2017).

Caregiver HRQoL

Data on caregiver HRQoL are available from a recent vignette study conducted by Pfizer using a time-trade-off (TTO) methodology; the study estimated the mean utility scores for eight DMD caregiver vignettes based on the health states as defined in the Project HERCULES (PH) Natural history model (NHM) (Pfizer UK 2024a). The study collected data via TTO interviews with 200 members of the UK general public to produce utility scores for caregivers of people with DMD [redacted] (Table 135) [redacted] The increasing demands and complexities

associated with DMD described above (such as boys/young men losing their ability to perform activities of daily living, requiring ventilation support, and assistance with mobility) consistently increase the burdens and expectations placed upon caregivers. These data reveal that the HRQoL [redacted].

Table 135: Mean utility scores and mean VAS scores through eight DMD HS carried out with members of general public

	HS1 Early ambulatory	HS2 Late ambulatory	HS3 Transfer	HS4 HTMF, no ventilation	HS5 No HTMF, no ventilation	HS6 HTMF, night-time ventilation	HS7 No HTMF, night-time ventilation	HS8 Full time ventilation
Utility score	0.72	0.67	0.58	0.56	0.50	0.54	0.51	0.48
VAS score	[redacted]							

[redacted].

Abbreviations: DMD: Duchenne muscular dystrophy; HS: health state; TTO: time-trade-off; VAS: visual analogue scale.
References: Pfizer Caregiver vignette study in DMD, 2024 (Pfizer UK 2024a)

Burden on siblings and the wider family

About one-third of parents believe that DMD has a negative influence on the psychological well-being and social life of the unaffected siblings (Magliano et al. 2014). Siblings often run the risk of being "voiceless" and may feel invisible to parents focused on the complex needs of their child with DMD (Duchenne Data Foundation 2022, Action Duchenne 2018). Siblings describe themselves as having to manage their emotional pain on their own, as they are unable to share it with a family system that is under significant pressure (Duchenne Data Foundation 2022). Many siblings give up time with friends, sports or extracurricular activities and/or travel (Schwartz et al. 2021, [redacted]). This can lead to practical and psychological difficulties for the sibling, including a negative impact on their social life (such as school performance and involvement in leisure activities) and their emotional well-being (such as fear, aggression, or withdrawal) (Reid and Alexander 2021). A recent burden of illness study in Denmark looked into the impact on siblings to a child with DMD (Rudolfsen et al. 2024). Siblings were found to have lower grades in high school, a higher unemployment rate, higher long terms sick leave than controls and also had higher use of inpatient care. Although not having data on quality of life, the data in the study showed the impact on elements in life that affect the wellbeing and health of the siblings. At the time of bereavement, the loss of a sibling

is a highly traumatic event and may be more disruptive than the loss of other family members (Huang et al. 2024).

Burden on school settings

The most significant changes in a child's physical ability will occur during their school years (FDA 2024, Muscular Dystrophy Assoc. 2024). Therefore, specialist support and adaptations or modifications to the classroom environment will be required to ensure children with DMD can reach their potential (FDA 2024, Muscular Dystrophy Assoc. 2024). In a study of school experiences of boys with DMD, non-ambulatory students had a significantly greater prevalence of needing a teaching assistant and additional support compared to those who were ambulating, suggesting that schools and local authorities need to plan to allocate greater resources for boys with DMD as they grow older and more physically disabled (Soim et al. 2016).

Economic burden of DMD

Cost of illness data, especially in non-ambulant children in real-world settings, is difficult to capture; however, overall, the economic burden of DMD is very high. The total annual costs of DMD encompass a spectrum of components, including hospital admissions, visits to physicians and practitioners, tests and assessments, medications, nonmedical community services, aids, devices, investments, informal care, and indirect costs.

Direct costs

The average cost based on international data associated with the care and treatment of boys and young men with DMD was estimated to be ten times higher than that of the cost incurred by the overall population in a cross-sectional study of boys and young men with DMD and their caregivers from Bulgaria, France, Germany, Hungary, Italy, Spain, Sweden, and the UK (Cavazza et al. 2016). In an international study that estimated the total cost of illness and economic burden associated with DMD, the annual mean per-patient direct costs for DMD were estimated at €42,360, €23,920, and €54,160, in Germany, Italy, and UK, respectively (Table 136) (Landfeldt et al. 2014).

Table 136: Estimation of total cost of illness and economic burden associated with DMD in three European Countries

Country	Annual Mean Per-Patient Direct Costs of DMD (€)	Annual Mean Household Burden of DMD (€)	Total Annual Economic Burden of DMD (€)
Germany	42,360	70,190	27M
Italy	23,920	58,440	1M
UK	54,160	63,600	200M

Abbreviations: DMD: Duchenne muscular dystrophy; M: Million; UK: United Kingdom.
References: Landfeldt et al. (2014).

Rehabilitation services (e.g. physiotherapy, occupational therapy, and speech and language therapy) and the costs of medical aids were shown to represent the main drivers for direct medical costs, accounting for 50% of the direct annual costs of DMD (Landfeldt et al. 2014). Costs increased after the loss of ambulation when patients

became full-time wheelchair users and required respiratory support (Landfeldt et al. 2014, Strober et al. 2023). The main drivers for nonmedical direct costs relate to community nursing support in the home and the costs associated with car and home adaptations required to accommodate the consequences of disease progression (Schreiber-Katz et al. 2014).

In an analysis of Hospital Episode Statistics (HES) data undertaken by the company, the majority of healthcare activity was delivered through outpatient appointments across all age groups (Figure 66) (Italfarmaco UK 2024). [redacted]

Figure 66: Proportion of acute and outpatient activity by age group, HES analysis

[redacted]

Indirect costs

DMD imposes substantial financial stress upon affected families, impacting productivity, employment status, and other aspects of life. Moreover, this impact on families and caregivers increases as the disease progresses (Porteous et al. 2021). The indirect costs of DMD are associated with household caregiving responsibilities and increase significantly as the disease progresses. In an international, cross-sectional study, the mean annual household burden for DMD was estimated at between €58,440 and €71,900. The costs vary across different countries, with Germany incurring €70,190, Italy €58,440, and the UK €63,600 in indirect costs. The total economic burden of DMD, including the monetary value of the loss in patient and caregiver QoL in Germany, Italy,

and the UK, was estimated at €278,058,000, €154,465,000, and €200,478,000, respectively (Table 136) (Landfeldt et al. 2014).

The same study reported that 89% of patients received part- or full-time care from another person who was the parent in 93% of the cases. Caregivers often resigned from their employment (30%), reduced working hours (38%) on average by 15 hours per week, and missed a mean of 14.5 working days per year due to their child's disease. In addition, 60% of caregivers expressed that their career pursuits were constrained, and 49% reported reduced earnings due to their son's condition (Schreiber-Katz et al. 2014).

Mortality costs

For diseases with no or minimal excess mortality, the costs incurred for living patients provide an adequate estimate of their economic burden to society. However, for diseases with a high mortality rate, such as DMD, the total aggregated national cost remains relatively low due to the disease's low prevalence, even though it places a substantial burden on individual patients. Consequently, diseases with high mortality may appear less costly to society despite the significant value of the life years lost. Therefore, mortality costs are a crucial factor when analysing the overall burden (Landfeldt et al. 2017b).

A 2012 study assessing the mean annual mortality cost of DMD in Germany, Italy, the UK, and the US estimated the life years lost due to DMD based on the incidence of the condition for each country and subsequently calculated the mortality cost using a willingness-to-pay of €75,000 per life-year gained. The study showed that the national mortality cost of DMD was €335M for Germany, €248M for Italy, €267M for the UK, and €1,208M for the US (Landfeldt et al. 2017b).

Health care consumption for DMD in the Nordics

A recent mapping study conducted by Oslo Economics for Norway confirms the overall high disease burden of DMD. Annual costs were estimated to NOK 75 million for direct healthcare, and even higher for production losses and informal care, NOK 125 million. The study highlights the vast impact of the disease, e.g. many patients require personal home assistance, aids such as wheelchairs, and school assistance. It concludes that DMD severely reduces life expectation and the quality of life of both patients and next of kin, estimating the total number of QALYs lost due to DMD in Norway during 2021 to 308 for patients alone (Oslo Economics 2023).

In Denmark, a study analysing health and administrative registers for 213 individuals with DMD confirms the high consumption of health care (Rudolfsen et al. 2024):

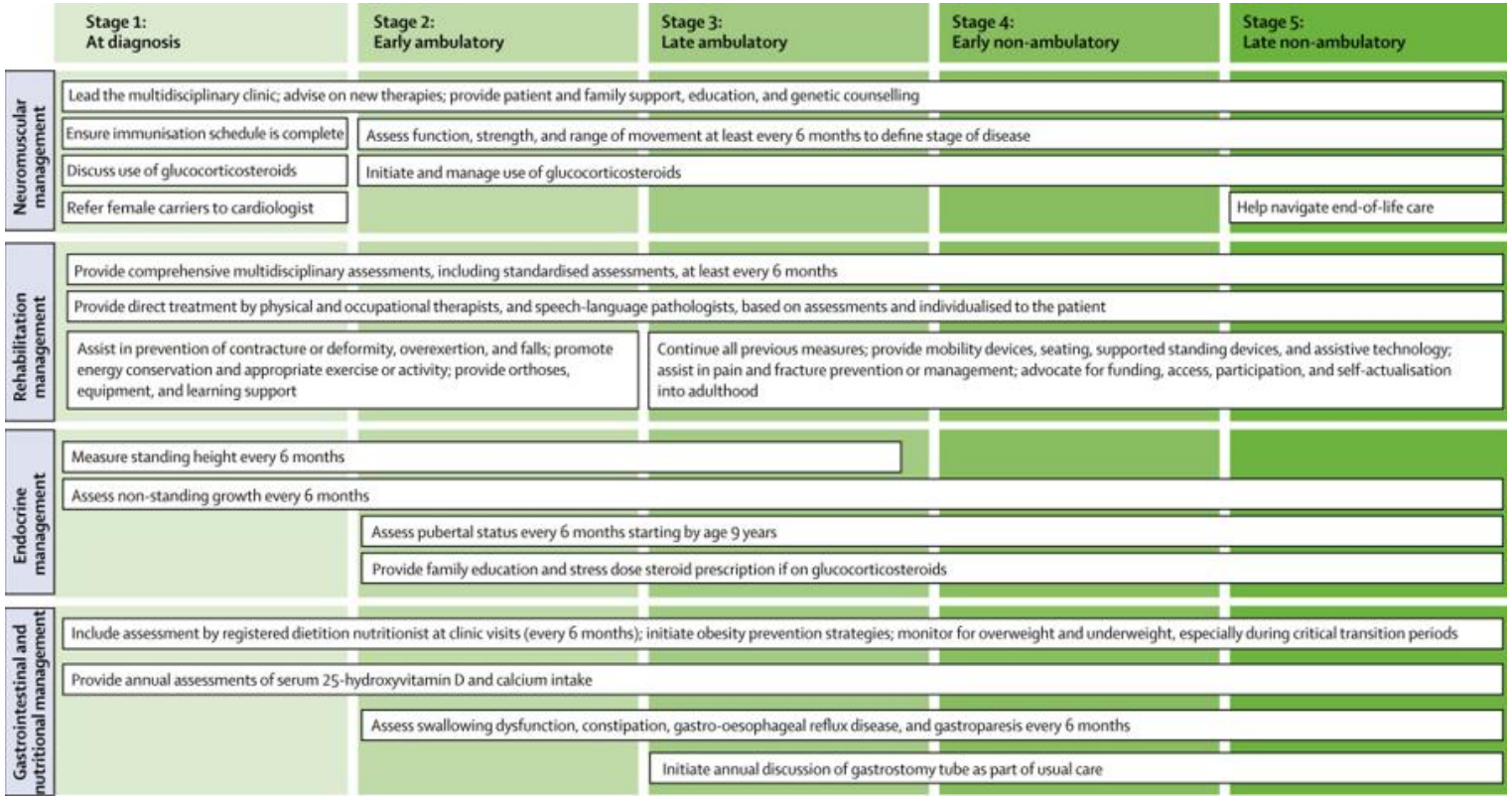
- Individuals with DMD had between two and seven hospital admissions more compared to their controls each year.
- In the 20 years after diagnosis, each individual with DMD had on average 60 additional hospital admissions and 200 additional outpatient contacts compared to their controls.

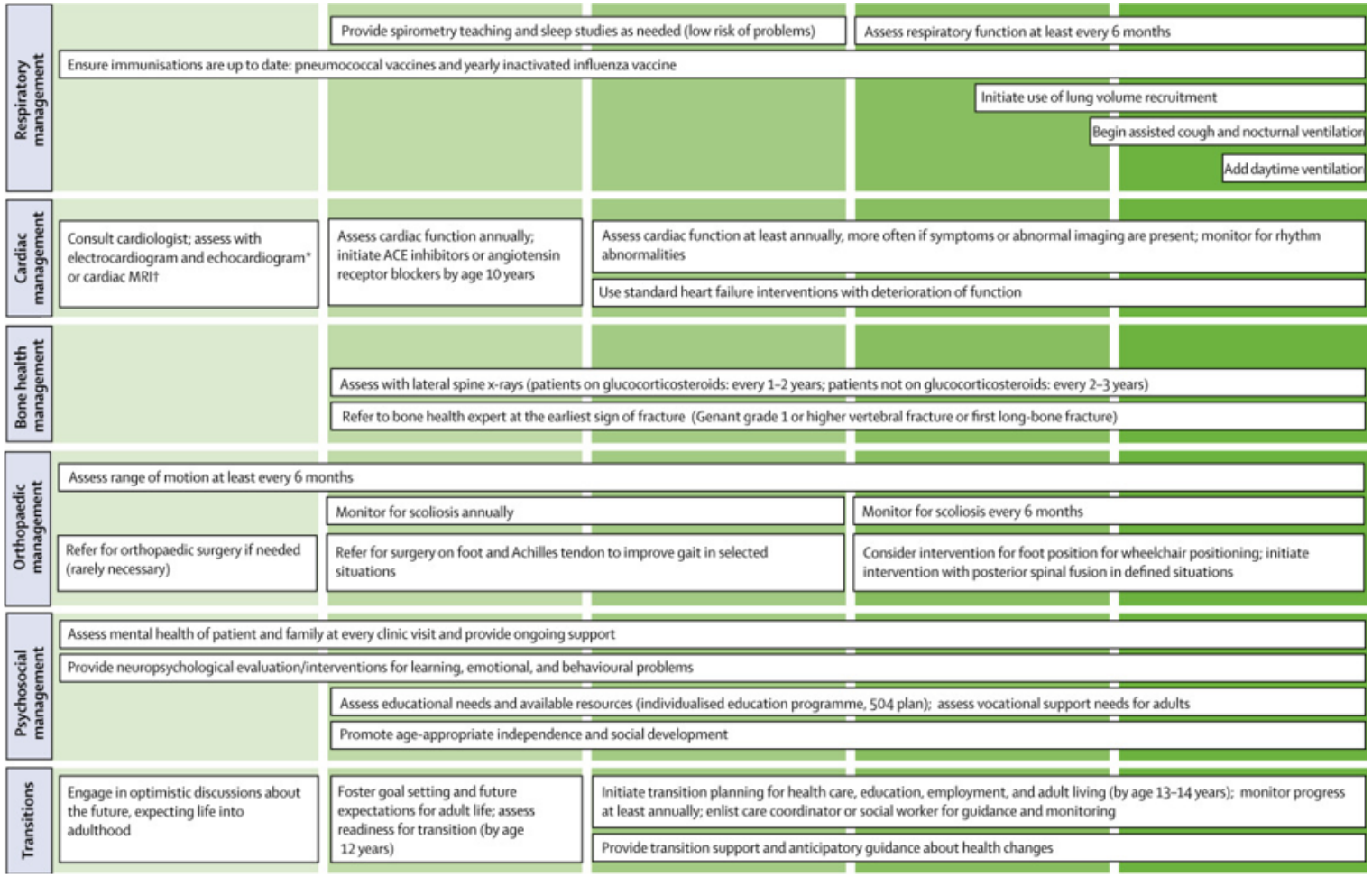
- Individuals with DMD received significantly more home care for personal care. The largest difference was found in year 14 after diagnosis, where they received 85 hours more on average than their control
- Mortality hazard was 23.3 times higher compared to matched controls.
- In total, 46 individuals with DMD died during the study period. Mean age at death was 26.8 years (IQR: 19–34).
- 73% of the study population with DMD was observed with respiratory failure, 67% was observed with dependency on assistive machines such as respirator or wheelchair, and 54% had a scoliosis diagnosis. For individuals with DMD, labour market participation was low, only 14.5% were observed with income in at least one year.
- The extra costs of healthcare services for DMD before an individual with DMD turns 18 years summed to EUR 452,100, while the extra costs reached EUR 1,922,000 if an individual lives to be 30 years old. When including special education and production loss, the total extra costs of an individual with DMD who lives to be 30 years old, summed up to EUR 2,365,800.

In a Swedish study using data from the National Registry for Neuromuscular Disorders (NMiS), the economic burden of DMD was assessed through a retrospective observational design (Ekström et al. 2024). Data from 211 patients diagnosed with DMD between January 2006 and December 2021 were analysed, with patients classified based on disease progression into ambulatory, transitional non-ambulatory, and fully ventilatory-supported stages. Direct and indirect costs were estimated, with annualized direct medical costs averaging €14,590 per patient, primarily due to prescribed drugs (€9,658, 66%). While direct costs decreased in later disease stages, indirect costs increased significantly, averaging €136,294 per year, with personal assistance (45%) and lost productivity (32%) as the main cost drivers. In advanced disease stages, indirect costs were up to four times higher than in earlier stages, emphasizing the escalating financial impact of disease progression. The findings suggested that novel treatments with the potential to slow disease progression may help mitigate long-term healthcare and societal costs.

Treatment guidelines

Figure 67: Comprehensive care of individuals with Duchenne muscular dystrophy




Respiratory management
Provide spirometry teaching and sleep studies as needed (low risk of problems)
Assess respiratory function at least every 6 months
Ensure immunisations are up to date: pneumococcal vaccines and yearly inactivated influenza vaccine
Initiate use of lung volume recruitment
Begin assisted cough and nocturnal ventilation
Add daytime ventilation
Cardiac management
Consult cardiologist; assess with electrocardiogram and echocardiogram* or cardiac MRI†
Assess cardiac function annually; initiate ACE inhibitors or angiotensin receptor blockers by age 10 years
Assess cardiac function at least annually, more often if symptoms or abnormal imaging are present; monitor for rhythm abnormalities
Use standard heart failure interventions with deterioration of function
Bone health management
Assess with lateral spine x-rays (patients on glucocorticosteroids: every 1–2 years; patients not on glucocorticosteroids: every 2–3 years)
Refer to bone health expert at the earliest sign of fracture (Genant grade 1 or higher vertebral fracture or first long-bone fracture)
Orthopaedic management
Assess range of motion at least every 6 months
Monitor for scoliosis annually
Monitor for scoliosis every 6 months
Refer for orthopaedic surgery if needed (rarely necessary)
Refer for surgery on foot and Achilles tendon to improve gait in selected situations
Consider intervention for foot position for wheelchair positioning; initiate intervention with posterior spinal fusion in defined situations
Psychosocial management
Assess mental health of patient and family at every clinic visit and provide ongoing support
Provide neuropsychological evaluation/interventions for learning, emotional, and behavioural problems
Assess educational needs and available resources (individualised education programme, 504 plan); assess vocational support needs for adults
Promote age-appropriate independence and social development
Transitions
Engage in optimistic discussions about the future, expecting life into adulthood
Foster goal setting and future expectations for adult life; assess readiness for transition (by age 12 years)
Initiate transition planning for health care, education, employment, and adult living (by age 13–14 years); monitor progress at least annually; enlist care coordinator or social worker for guidance and monitoring
Provide transition support and anticipatory guidance about health changes

Care for patients with Duchenne muscular dystrophy is provided by a multidisciplinary team of health-care professionals; the neuromuscular specialist serves as the lead clinician. The figure includes assessments and interventions across all disease stages and topics covered in this three-part Review.

*Echocardiogram for patients 6 years or younger. †Cardiac MRI for patients older than 6 years.
References: Birnkrant et al. (2018c), Birnkrant et al. (2018a), Birnkrant et al. (2018d)

Appendix M. Transition probabilities used in the model

Model structure

The model had the following health states:

- **Health State 1** - Early ambulatory: The patient can stand from supine and can walk/run 10 m
- **Health State 2** - Late ambulatory: The patient can no longer stand from supine but can still walk/run 10 m
- **Health State 3** – Transfer: The patient can no longer walk/run 10 m but can still (remain) standing for 3 s (NSAA item 1—stand: score of 1 or 2)
- **Health State 4** - Hand-to-mouth function and no ventilator: The patient can no longer (remain) standing for 3 s (NSAA item 1—stand: score of 0); The patient has a hand-to-mouth function (Brooke score ≤ 4a); The patient is not on a ventilator (FVC% ≥ 50%)
- **Health State 5** - No hand-to-mouth function and no ventilator: The patient has no hand-to-mouth function (Brooke score > 4); The patient is not on a ventilator (FVC% ≥ 50%)
- **Health State 6** - Hand-to-mouth function and night-time ventilator: The patient has hand-to-mouth function (Brooke score ≤ 4); The patient is on night-time ventilation (30% ≤ FVC% < 50%)
- **Health State 7a/7b** - No hand-to-mouth function and night-time ventilator: The patient has no hand-to-mouth function (Brooke score > 4); The patient is on night-time ventilation (30% ≤ FVC% < 50%)
- **Health State 8a/8b** - No hand-to-mouth function and full-time ventilator: The patient has no hand-to-mouth function (Brooke score > 4); The patient is on full-time ventilation (FVC% < 30%)
- **Death**

The “transfer state,” deemed crucial by patients and caregivers, marks a stage in the progression of DMD where patients lose the ability to walk but can still support their weight for specific movements, such as transfers between a wheelchair and a toilet. The recognition of this state acknowledges its impact on QoL, care support requirements, and costs. Once patients lose this ability, there is an increased burden on caregivers and a need for additional resources. This health state is the key addition to this model compared with NHMs previously described in the literature (Mercuri et al. 2024b).

Natural history transition probabilities

Table 137 presents the number (%) of transitions observed from one state to another in the D-RSC dataset; Transitions from health state 1 represented the largest percentage of

transitions observed ([70.8%]); observations in health states 1 and 2 (early and late ambulatory patients) comprised 81.3% of observed transitions. The greatest number of transitions observed were in patients remaining in state 1 (the early ambulatory state; 67.4% of observed transitions) while there were very few transitions observed into or out of state 3 (the new "transfer state"). There were no data pertaining to transitions into state 4 (the first non-ambulatory state) or out of state 4 into states 5 and 6, as no patients were observed in state 4 in the D-RSC dataset (Broomfield et al. 2024).

The transition probabilities for the NHM were estimated following six steps (Broomfield et al. 2024):

- The mean age of patients observed in each state in the D-RSC data was estimated
- To estimate the mortality rate for each state, a piecewise constant hazard function was fitted to the mortality data, with cut points determined by mean age in each state
- The initial values of a transition intensity matrix were specified using the estimated mortality rates and setting transition intensities for all transient states to 0.1
- A multistate model was fitted in R using the msm package using the transition intensity matrix and fixing mortality rates at their initial values
- A new transition intensity matrix was then defined using the transition intensities estimated in Step 4 and mortality rates estimated in Step 2.
- Steps 4 and 5 were repeated using the newly defined transition intensity matrix until the model converged

Convergence was defined as transition rates being equal to 4 decimal places. An exponential distribution (i.e. constant transition intensities) was used to fit the multistate model for transitions up to health states defined by the requirement for full-time ventilation. A piecewise exponential distribution was assumed for transitions from full-time ventilation states to death. Initial consideration of the exponential distribution for all transitions led to an implausibly long length of stay in the full-time ventilation states. This was due to the long tails associated with the exponential distribution and a fixed mortality rate (Broomfield et al. 2024).

Due to the paucity of data about health states 3,4, 5, and 6 in the dataset, an elicitation approach was used to inform transition intensities. The information was elicited from four clinicians and four caregivers involved in the PH collaboration and followed by an online survey of Duchenne UK with 20 responses from DMD parents, caregivers, and practitioners. Respondents were asked to describe the average age at which patients enter and exit health states. Based on the response the mean and SD of age were estimated (Broomfield et al. 2024).

The NHM including the transfer state converged after two iterations.

Table 138 presents the transition probabilities estimated by the updated NHM following the adjustments described above – these are applied for SoC in the CEM. Transition intensities including and excluding the transfer state are presented in Table 139 and Table 140, respectively.

Table 137: Transitions Observed in the C-Path-D-RSC Dataset (%)

From	To>1	2	3	4 *	5	6	7	8	Total
1	2991 (67.0)	158 (3.5)	4 (0.1)	-	3 (0.1)	6 (0.1)	1 (< 0.1)	1 (< 0.1)	3164 (70.8)
2	21 (0.5)	404 (0.9)	4 (0.1)	-	15 (0.3)	20 (0.5)	3 (0.1)	3 (0.1)	470 (10.5)
3	-	1 (< 0.1)	8 (0.2)	-	-	-	-	-	9 (0.2)
4	-	-	-	-	-	-	-	-	-
5	-	-	-	-	79 (1.8)	5 (0.1)	34 (0.8)	5 (0.1)	123 (2.8)
6	-	2(< 0.1)	-	-	5 (0.1)	108 (2.4)	24 (0.5)	16 (0.4)	155 (3.5)
7	-	-	-	-	7 (0.2)	10 (0.2)	118 (2.6)	47 (1.1)	182 (4.1)
8	-	-	-	-	1 (< 0.1)	1 (< 0.1)	6 (0.1)	356 (8.0)	364 (8.2)
Total	3012 (67.4)	565 (12.7)	16 (0.4)	-	110(2.5)	150 (3.4)	186 (4.2)	428 (9.6)	4467

Note: *No patients were observed in state 4 in the D-RSC dataset.

Table 138: Transition probabilities from the updated NHM

From/To	State 1	State 2	State 3	State 4	State 5	State 7A	State 8A	State 6	State 7B	State 8B	State 9
State 1	98.01%	1.99%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
State 2	0.00%	96.98%	0.00%	3.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.02%
State 3	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
State 4	0.00%	0.00%	0.00%	96.42%	1.79%	0.00%	0.00%	1.72%	0.00%	0.00%	0.06%
State 5	0.00%	0.00%	0.00%	0.00%	98.17%	1.70%	0.00%	0.00%	0.00%	0.00%	0.13%
State 7A	0.00%	0.00%	0.00%	0.00%	0.00%	96.45%	3.28%	0.00%	0.00%	0.00%	0.28%
State 8A	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	98.76%	0.00%	0.00%	0.00%	1.24%
State 6	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	98.23%	1.53%	0.00%	0.25%
State 7B	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	95.63%	4.09%	0.28%
State 8B	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	98.76%	1.24%
State 9	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	100.00%

Abbreviations: NHM: Natural history model

Table 139: Matrix of Transition Intensities Including the Transfer Health State

From/To	State 1	State 2	State 3	State 4	State 5	State 7A	State 8A	State 6	State 7B	State 8B	State 9, age below 30 years	State 9, age above 30 years
State 1	0	0.25	0	0	0	0	0	0	0	0	0.00	0.00
State 2	0	0	0.45	0.00	0	0	0	0	0	0	0.00	0.00
State 3	0	0	0	1.01	0	0	0	0	0	0	0.00	0.00
State 4	0	0	0	0	0.29	0	0	0.28	0	0	0.01	0.01
State 5	0	0	0	0	0	0.20	0	0	0	0	0.01	0.01
State 7A	0	0	0	0	0	0	0.40	0	0	0	0.03	0.03
State 8A	0	0	0	0	0	0	0	0	0	0	0.15	0.15
State 6	0	0	0	0	0	0	0	0	0.18	0	0.03	0.03
State 7B	0	0	0	0	0	0	0	0	0	0.50	0.04	0.04
State 8B	0	0	0	0	0	0	0	0	0	0	0.15	0.15
State 9	0	0	0	0	0	0	0	0	0	0	0	0

Table 140: Matrix of Transition Intensities Excluding the Transfer Health State

From/To	State 1	State 2	State 3	State 4	State 5	State 7A	State 8A	State 6	State 7B	State 8B	State 9, age below 30 years	State 9, age above 30 years
State 1	0	0.24	0	0	0	0	0	0	0	0	0.00	0.00
State 2	0	0	0.00	0.37	0	0	0	0	0	0	0.00	0.00
State 3	0	0	0	0.00	0	0	0	0	0	0	0.00	0.00
State 4	0	0	0	0	0.22	0	0	0.21	0	0	0.01	0.01
State 5	0	0	0	0	0	0.21	0	0	0	0	0.02	0.02
State 7A	0	0	0	0	0	0	0.40	0	0	0	0.03	0.03
State 8A	0	0	0	0	0	0	0	0	0	0	0.15	0.15
State 6	0	0	0	0	0	0	0	0	0.19	0	0.03	0.03
State 7B	0	0	0	0	0	0	0	0	0	0.50	0.03	0.03
State 8B	0	0	0	0	0	0	0	0	0	0	0.15	0.15
State 9	0	0	0	0	0	0	0	0	0	0	0	0

Appendix N. Additional studies

Study Study 43 (Phase I/II)

Study design

Study 43 is a two-part Phase I/II open-label study to assess safety and tolerability, PK and effects on histology, and different clinical parameters of Duvyzat® (givinostat) in ambulant patients from 7 years old to less than 11 years old with DMD. A total of 20 patients were included in the study (ClinicalTrials.gov 2023c, Bettica et al. 2016). A total of 20 patients were included in the study (ClinicalTrials.gov 2023c, Bettica et al. 2016).

Study 43 – Part 1

In Part 1 of the study, patients were treated with three different dosing regimens (Figure 68) (ClinicalTrials.gov 2023c):

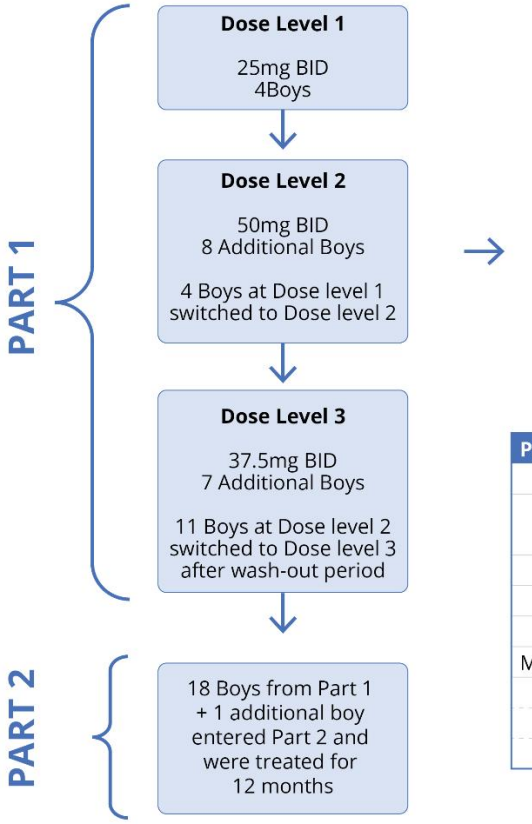
- Low dose: the first four children were treated at a low dose of Duvyzat® (givinostat) (25 mg BID for children weighing between 20 kg and 49 kg and 37.5 mg BID for those weighing ≥50 kg)
- Intermediate dose: if none of the discontinuation criteria were met after 2 weeks of treatment at the low dose, the review committee was asked to determine the increased dose to be used for the treatment of the additional eight patients who were to be treated at the intermediate dose
- High dose: if none of the discontinuation criteria were met after 2 weeks of treatment at the intermediate dose, the review committee was to determine the subsequent dose to be used for the treatment of the additional eight children who were to be treated at the high dose. All children treated at the intermediate dose were also to be treated at the highest dose

In Part 1 of the study, patients had a visit to the centre every week (ClinicalTrials.gov 2023c).

Study 43 – Part 2

After at least 2 weeks of treatment, for the 20 patients who were enrolled in Part 1 of the study, the review committee was asked to determine the recommended dose to be used for Part 2 of the study based on safety, tolerability and the PK profile obtained. All patients included in Part 2 of the study were then treated at the recommended dose, administered for the next 12 months. During Part 2, patients had a total of 10 visits to the centre (Figure 68) (ClinicalTrials.gov 2023c).

Figure 68: Study design and patient demography



Parameter	Overall (N=20)
Age (years), Mean	8.2
6MWD (m), Mean (SD)	458.0 (64.49)
Height (cm), Mean	121.5
Weight (kg), Mean	27.0
BMI (kg/m^2), Mean	18.1
Mutation Type	
Deletions, N(%)	10 (50.0)
Duplications, N(%)	5 (25.0)
Point Mutations, N(%)	5 (25.0)

Abbreviations: BID: Twice daily; N: number of patients in the study population
References: Bettica et al. (2016)

Study population

The primary inclusion and exclusion criteria comprised the following (Table 141): (ClinicalTrials.gov 2023c)

Table 141: Study 43 inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Male patients aged 7 to <11 years with an immunohistochemical and molecular diagnosis of DMD • Able to complete the 2 6MWDs tests at selection with a minimal distance of at least 250 meter each. In addition, the results of these tests must be within ±30 meters of each other • On a stable dose of systemic GCs for at least 6 months	• Initiation of systemic GC therapy within 6 months prior to the start of study drug or change in systemic GC therapy (e.g., initiation, change in type of drug, dose modification not related to body weight change, schedule modification, interruption, discontinuation, or re initiation) within 6 months prior to the start of study drug • Use of any pharmacologic treatment, other than GCs, that

- At least 6 months' worth of data on the 6MWD (this will be the "historical" 6MWD). From the moment of the historical 6MWD assessment(s), the patient must not have received any compound that could potentially affect the 6MWD, with the exception of the stable GC treatment

might have an effect on muscle strength since the time of the historical 6MWD and in any case within 3 months prior to the start of study treatment (e.g., growth hormone). Vitamin D, calcium, and integrators will be allowed

- Surgery that might have an effect on muscle strength or function within 3 months before study entry or planned surgery at any time during the study
- Exposure to another investigational drug since the time of the historical 6MWD and in any case within 3 months prior to the start of study treatment
- History of participation in gene therapy, cell-based therapy or oligonucleotide therapy
- Presence of other clinically significant disease that in the opinion of the investigator places the patient in unacceptable risk for an adverse outcome or that could affect study results
- Symptomatic cardiomyopathy or heart failure. If patient has a left ventricular ejection fraction <45% at screening, the investigator should discuss inclusion of patient in the study with the medical monitor
- Inadequate hematological function
- Absolute neutrophil count: <1.5 x 109/L
- Platelets: <100 x 109/L
- Current or history of liver disease or impairment, including but not limited to an elevated total bilirubin
- Inadequate renal function, as defined by serum creatinine >2 x the upper limit of normal
- Positive test for hepatitis B surface antigen, hepatitis C antibody, or

	human immunodeficiency virus at screening • A baseline QTc >450 msec, (as the mean of 3 consecutive readings 5 minutes apart) or history of additional risk factors for torsades de pointes (e.g., heart failure, hypokalemia, family history of long QT syndrome) • Psychiatric illness/social situations rendering the potential patient unable to understand and comply with the study protocol

Abbreviations: 6MWD: 6-minute walking distance; DMD: Duchenne Muscular Dystrophy; GCs: glucocorticoids

References: ClinicalTrials.gov (2023c)

Study endpoints

The primary objective of Study 43 was to assess whether Duvyzat® (givinostat) could extend its beneficial histological effects to DMD patients, confirming its ability to counteract histological signs of the disease in humans by evaluating muscle biopsies from baseline to the end of treatment. The secondary key objectives included assessing the safety, tolerability and functional assessments (Bettica et al. 2016, Cazzaniga et al. 2018).

The primary endpoint of Study 43 was the change in histology comparing the brachial bicep biopsies before and after ≥12 months of treatment with Duvyzat® (givinostat). The histological parameters assessed were the muscle fibre area fraction (MFAF), CSA, necrosis, hypercontracted (hyaline) fibres, fatty replacement and fibrosis (total, endomysial, perimysial) (Bettica et al. 2016).

Secondary endpoints were (assessed after 12 months of treatment) as follows:

- Variation in several histological criteria (muscle fibre area, inflammation, necrosis, fibrosis, and muscle regeneration),
- Variation in muscle function assessed by the 6MWD,
- Change in muscle function as assessed by the NSAA score,
- Change in muscle function as assessed by the PUL score.

The criteria for the 6MWD, NSAA, and PUL were also assessed during the extension phases after 24, 36, and 52 months of Duvyzat® (givinostat) treatment. The number of TEAEs and serious adverse events (SAEs) after 24, 36, and 52 months were also assessed (Bettica et al. 2016, ClinicalTrials.gov 2023c).(Bettica et al. 2016, ClinicalTrials.gov 2023c).

Analysis sets

The ITT population included all patients who were enrolled in the Part 1 portion or entered the Part 2 portion of the study (Table 142). Patients were analysed according to

the dose level to which they were allocated. Twenty patients were included in the ITT population (Italfarmaco 2019).

The completers population included all patients who successfully completed the Part 2 portion of the study. Patients were analysed according to the dose level of which they were allocated. Nineteen patients were included in the completer's population (Table 142)(Italfarmaco 2019).

Table 142: Datasets analysed: ITT population

Parameter	25 mg BID (N=4)	37,5 mg BID (N=8)	50 mg BID (N=8)	Total (N=20)
ITT Analysis Population, N (%)	4 (100)	8 (100)	8 (100)	20 (100)
Safety Analysis Population (Part 1), N (%)	4 (100)	7 (100)	8 (100)	19 (100)
Safety Analysis Population (Part 2), N (%)				19 (100)
Completers Population	4 (100)	8 (100)	7 (87,5)	19 (95)
Evaluable Analysis Population	3 (75)	8 (100)	7 (87,5)	18 (90)
PK Analysis Population (Part 1)	4 (100)	7 (100)	8 (100)	19 (100)
PK Analysis Population (Part 2)a	12 (100)	7 (100)		19 (100)

Notes: [a]Part 2: group defined with actual dose at Visit 10

Abbreviations: BID: twice daily; ITT: intention-to-treat; N: number of patients in the study population; PK: pharmacokinetic

References: Italfarmaco (2019)

The ITT Analysis Population, set up for 19 patients (100%) during Extension 1, and for 18 patients (100%) during Extension 2 and Extension 3. In all Extensions, the Safety Analysis Population was set up for 20 patients (100%), including all patients who received any investigational product (Italfarmaco 2019).

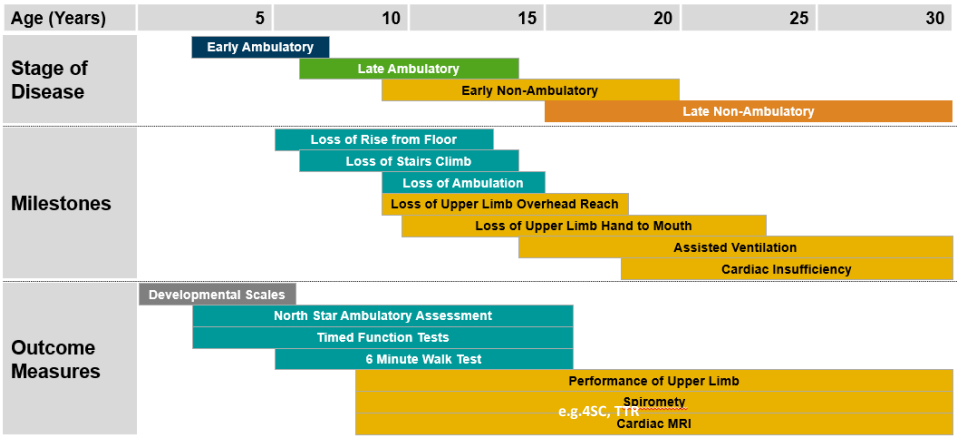
Appendix O. Miscellaneous

Validation of outcomes

Due to its long-term degenerative nature, directly demonstrating treatment effects on lifetime outcomes within a single RTC placebo-controlled trial is unfeasible. Consequently, therapeutic strategies prioritize slowing disease progression and preserving muscle function, and delaying milestones (Birnkrant et al. 2018a, Birnkrant et al. 2018c). Given that lost muscle cannot be restored, early intervention is critical. Timed functional tests, such as the 4SC or the NSAA tests, serve as predictors of losing ambulatory capacity (LoA) (Bushby and Connor 2011, McDonald 2018). Patients who lose ambulation at a younger age tend to experience an earlier onset and more rapid progression of respiratory muscle weakness (Mayer 2019). FVC, a measure of respiratory function, has been shown to decline progressively in individuals with DMD. Reduced FVC is associated with increased morbidity and mortality, making it a critical parameter for monitoring disease progression and the effectiveness of therapeutic interventions (Phillips et al. 2001, Sawnani et al. 2019).

In EPIDYS, study endpoints consisted of timed functional test, muscle strength, imaging test (MRS) and safety. Functional test are predictors of disease milestones indicative of disease progression, such as loss of ability to rise from the floor (TTR), climb stairs and walk unassisted (4SC) predict LoA, (Figure 69). These disease milestones also correlate with specific stages of the disease. Measures of strength, timed motor performance, and pulmonary function have been well described and validated by clinicians and clinical researchers in DMD. Timed motor performance evaluations such as the TTR, 4SC and the time to walk/run 10 metres (10MWT) are commonly used as clinical trial outcome measures, are reliable measures of functional ability, are endorsed by DMD clinical guidelines and regulatory agencies and have been used widely in DMD clinical trials (Figure 69) (Bushby and Connor 2011, Lynn et al. 2015).

Figure 69: Correlation of stages of DMD with milestones and outcomes measures



Abbreviations: DMD: Duchenne muscular dystrophy; MRI: Magnetic Resonance Imaging.
References: Adapted from Lynn et al. (2015).

The 4SC test, primary endpoint of EPIDYS, is a clinically meaningful, reliable and validated timed motor function test that is a widely used clinical study endpoint in DMD (Duong et al. 2021, McDonald et al. 2013a, McDonald 2018, Brooke et al. 1989), and is required by the EMA 2015 and Food and Drug Administration 2018 Guidelines. It is widely used as an endpoint in DMD trials and has shown to be predictive of DMD progression milestones, including LoA, loss of ability to climb stairs over two years and time to 10% decline in ambulatory capacity (Table 59, Appendix 0) (Bushby and Connor 2011).

The 4SC test objectively measures a clinically meaningful 'lifechanging' impact on a patient's overall health, as well as being predictive of future decline (Bushby and Connor 2011, McDonald 2018). In EPIDYS, the measurement was performed by qualified functional evaluators (physiotherapists) in a standardised manner (Italfarmaco 2023). Climbing stairs requires lower limb muscle strength and a range of motion from the leg joints; even small differences in 4SC are multiplied many times across a day for a child with DMD. Although 4SC has been used as an endpoint in DMD studies for decades, as it is reproducible and simple to administer, it is less widely used in clinical practice due to a lack of standardised equipment outside of research centres.

The key secondary endpoints (cumulative loss of function in the NSAA, change in TTR, change in the 6-minute walking distance [6MW] and change in strength) include the parameters that are considered relevant in this population to corroborate the results obtained from the primary 4SC endpoint (Italfarmaco 2022a).

Givinostat mechanism of action

As outlined in Appendix 0, HDAC has been identified to have a crucial role in the pathophysiology of DMD. Givinostat is a novel class I and II zinc-dependent HDACi orally administered that by modulating aberrant gene expression and cell signalling in the muscle, restores muscle homeostasis and promotes muscle regeneration in patients

affected by DMD. Givinostat reduces inflammation, muscle cell injury, intramuscular fibrosis and fatty replacement while promoting myogenesis in patients with DMD (Cazzaniga et al. 2018, Licandro et al. 2021).

The discovery that dystrophin deficiency leads to constitutive HDAC hyperactivation in muscle tissue has provided a strong rationale for investigating HDAC inhibitors, such as givinostat, as potential therapeutic agents for DMD (Lamb, 2024). Given that constitutive HDAC hyperactivity contributes to the exacerbation of muscle damage and impaired muscle repair and regeneration processes, its inhibition has the potential to restore muscle repair and attenuate disease pathology.

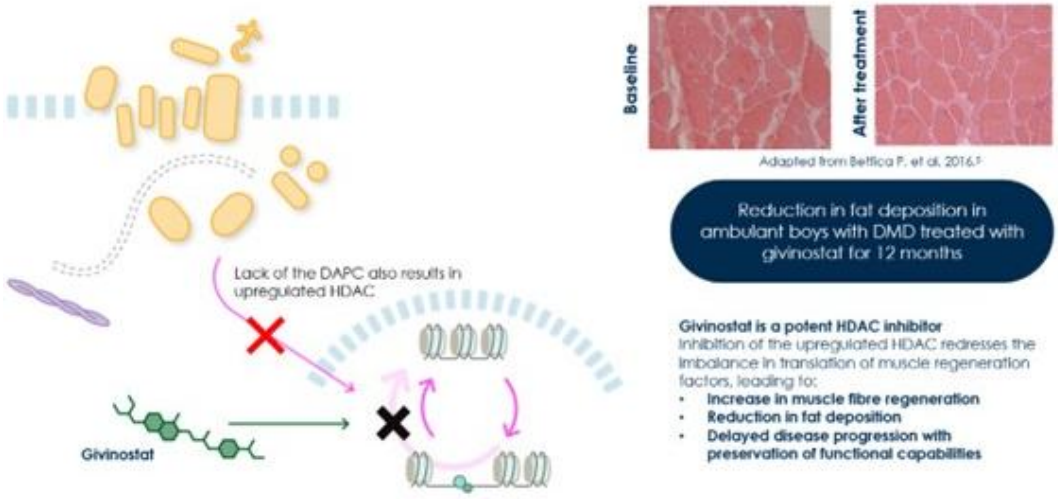
Notably, the inhibition of Class I and II HDAC isoforms has demonstrated beneficial effects on dystrophin-deficient muscle by reducing inflammation, restoring the expression of key proteins and microRNAs (miRNAs) involved in skeletal muscle homeostasis, and promoting the differentiation of muscle stem cells (MuSCs) into new muscle fibers. This mechanism of action positions HDAC inhibition as a promising therapeutic approach for DMD, addressing key pathological consequences of dystrophin deficiency without directly correcting the underlying genetic defect (Sandonà et al., 2023a).

Mechanistically, excessive HDAC activity in DMD, means that too many acetyl groups are removed from the histones and that the DNA is too tightly wrapped, which prevents expression of genes and failure to produce specific proteins (Aartsma-Rus 2025). Specifically for muscle damage repair this means the immune response gets ‘out of control’, and fibro-adipogenic stem cells get stuck in connective tissue production mode and become fibroblasts and fat cells, instead of supporting the muscle stem cells to differentiate and repair muscle. Furthermore, muscle stem cells can not differentiate and can no longer repair muscle. In addition to histones, other proteins are also regulated by the addition and removal of acetyl groups, which can further exacerbate muscle damage and pathology in DMD (Aartsma-Rus 2025).

Givinostat is a novel class I and II zinc-dependent HDACi orally administered that by modulating aberrant gene expression and cell signalling in the muscle, restores muscle homeostasis and promotes muscle regeneration in patients affected by DMD. Givinostat reduces inflammation, muscle cell injury, intramuscular fibrosis and fatty replacement while promoting myogenesis in patients with DMD (Cazzaniga et al. 2018, Licandro et al. 2021).

The givinostat mediated inhibition of HDAC hyperacetylation re-establishes the expression of proteins in muscle cells from boys and young men with DMD and miRNAs essential for restoring skeletal muscle homeostasis and activating muscle stem cells, to improve muscle repair (Figure 70) (Aartsma-Rus 2025, Sandonà et al. 2023b). The inhibition of HDAC hyperacetylation thus re-establishes the expression of proteins in muscle cells from DMD patients and miRNAs essential for restoring the skeletal muscle homeostasis and triggering the activation of MuSCs (Sandonà et al. 2023a).

Figure 70: Mechanism of action of givinostat



Abbreviations: DAPC: Dystrophin-associated Protein Complex; HAT: Histone acetyltransferases; HDAC: Histone deacetylase; HDACi: Histone deacetylase inhibitor.
References: Consalvi et al. (2011), Kodippili and Rudnicki (2023), Mercuri et al. (2024b), ClinicalTrials.gov (2023a), Bettica et al. (2016), Wilson et al. (2022), Campbell and Kahl (1989), Guiraud et al. (2015), Reid and Alexander (2021), Ervasti and Campbell (1993).

Medicinrådet

Danish Medicines Council
Secretariat
Dampfærgevej 21-23, 3rd floor
DK-2100 Copenhagen Ø

+ 45 70 10 36 00
medicinraadet@medicinraadet.dk

www.medicinraadet.dk