Medicinrådet

Bilag til Medicinrådets vurdering af vamorolon til behandling af Duchennes muskeldystrofi hos patienter fra 4 år

Vers. 1.0

Bilagsoversigt

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

NOTAT to Draft Assessment Report for vamorolone (AGAMREE)

Thank you for the opportunity to comment on the updated draft assessment report sent on 16-Feb-26. The last part of the DMC process has been highly irregular with significant changes in DMC's assessment of the health economic model after receipt of first draft assessment 09-Jan, and the corresponding proposed confidential rebate, and commenting; changes reflected in the presented ICERs increased >10x. The updated assessment of some assumptions conducted by DMC is still very difficult for us to interpret. The DMC ICER calculations differ significantly from other HTA agencies, and we cannot reproduce the findings.

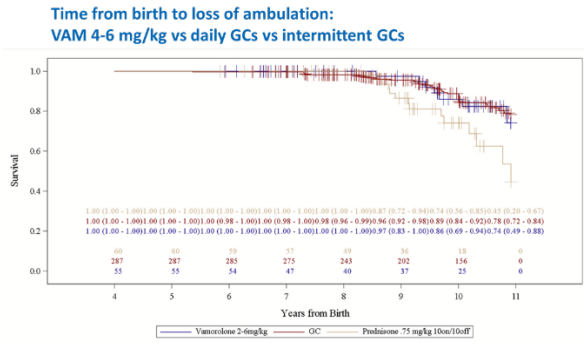
It can also be noted that the C/E analysis does not reflect the societal and human burden of this devastating disease. Especially in rare diseases, uncertainties in modelling are inherent. The now available long-term data analyses significantly reduce uncertainty and demonstrate the true value of vamorolone treatment.

To account for any remaining uncertainty and to ensure that the boys living with DMD in need of a corticosteroid allowing them to grow while preserving functional capabilities, we suggest recommendation of initiation of vamorolone in **1) ambulatory DMD boys 4-7 years, and 2) second line in DMD boys who experience significant side effects on classic corticosteroids, and cannot tolerate the recommended daily dose. We accept to offer this at the already negotiated confidential price**.

Similar efficacy between vamorolone and classic glucocorticoids

As background, vamorolone was developed by DMD experts to have equal efficacy but less side effects than the classic corticosteroids (CS). The entire preclinical development was targeted at finding a drug candidate with that profile.

We would like to highlight that the pivotal VISION-DMD study was powered against placebo. For the predefined primary outcome measure TTSTAND (time to stand from supine), there is 1) significant and clinically relevant improvement compared to placebo, 2) no significant change to 0.75 mg/kg/d prednisone (direct comparison), 3) no significant change to prednisone 0.75 mg/kg/d or deflazacort 0.9 mg/kg/d (indirect comparison). That one of many secondary end point analyses (TTCLIMB) is statistically significant can be given little weight given the number of tests. Similar efficacy is now further confirmed by very recent long-term data analysis (median time on vamorolone 5 y), where patients treated with vamorolone had **time to loss of ambulation** comparable to classic CS (=0.9041)[1].



[1] McDonald C et al. Comparative analysis of long-term effectiveness of vamorolone vs standard of care glucocorticoid (SoC GC) treatment in boys with DMD. Poster #23S, MDA Mar 2026.

In their publicly available HTA reports, both, England's NICE and the German G-BA find vamorolone as effective as prednisone.

With intermittent dosing schemes and/or doses lower than 0.75 mg/kg/d for prednisone/prednisolone and lower than 0.9 mg/kg/d for deflazacort the current Danish clinical practice is accounting for the side effects of classic CS (including growth stunting) **and significantly deviating from the studied dose of 0.75mg/kg/d prednisone**. Hence, in a real world setting, same effectiveness must be assumed.

Maintained growth

One key benefit of treatment of DMD with vamorolone is that it allows patients to not only stay on a CS dose high enough to remain efficacious, but continue growing; with solid demonstration of maintained height growth over up to 2.5 years as presented in Figure 7 in the report and now recently even confirmed up to 5 years vs classic CS ($p<0.0001$)[1]).

Bone health leads to reduced fracture risk

The draft assessment report highlights the uncertainty whether the maintained bone health (measured by bone turnover biomarkers) will translate into meaningful clinical outcomes. Clinically meaningful outcome has now been confirmed by very recent long-term data analysis (median time on vamorolone 5 y), where patients treated with vamorolone experienced a significantly lower rate of vertebral fractures compared to classic corticosteroids (8.1% vs 41.9%, $p=0.0082$)[2] .

Health economic assessment

After receiving DMC's draft assessment report 09-Jan, significant changes were made to some assumptions, including a clinical assumption on treatment length in Danish clinical practice. In the first report, based on the clinical expertise gathered during the assessment, DMC assessed that it is likely that treatment length of vamolorone would be similar to that of prednisolone. Given the largest data set on dosing of DMD patients (CINRG), this would correspond to an average treatment length of approximately 10 years. DMC updated this assumption in the report now published, and states that treatment with prednisolone and deflazacort is life-long, which is in contrast to insights from Prof. Vissing, that about 50% of DMD patients have fully stopped CS treatment before age of 18 years and are unwilling to restart due to side effects, and many are on reduced doses if on treatment. Communication with Muskelsvindfonden supports this.

Another key change made to the health economic model, after the 09-Jan draft report, is the impact on life years gained with vamolorone. Due to the enhanced side effect profile of vamolorone, patients may be able to maintain higher, optimal and efficacious doses than when treated with classic CS. As reflected in Danish clinical practice, many patients on classic CS need to decrease the dose or move to intermittent dosing due to side effects, which compromise the efficacy. Recent long-term data suggest that patients remained on higher vamolorone doses during the observation period. Patients remaining on optimal CS doses for longer delay the disease progression; they delay the loss of mobility, enhance upper limb function, pulmonary function, cardiac function and need for scoliosis surgery and ventilation. Furthermore, as highlighted by DMD Care UK corticosteroid standard-of-care guideline, long-term CS treatment is associated with prolonged survival.

[2] Guglieri M et al, Long-term impact of vamorolone on bone health compared to standard of care glucocorticoids (SoC GC) in boys with Duchenne Muscular Dystrophy (DMD). Poster #62S, MDA Mar 2026.

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MBA/KLE

Forhandlingsnotat

Dato for behandling i Medicinrådet	18.02.2026
Leverandør	Santhera Pharmaceuticals
Lægemiddel	Agamree (vamorolon)
Ansøgt indikation	Behandling af Duchennes muskeldystrofi (DMD) hos patienter på 4 år og derover.
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende pris på Agamree (vamorolon):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Agamree	40 mg/ml (100 ml oral suspension)	41.047,00	[redacted]	[redacted]

Prisen er betinget af Medicinrådets anbefaling.

Det betyder, at hvis Medicinrådet ikke anbefaler Agamree, indkøbes lægemidlet til AIP.

Aftaleforhold

[redacted] Leverandøren har mulighed for at sætte prisen ned i hele aftaleperioden.

Informationer fra forhandlingen

[redacted]

Konkurrencesituationen

I Medicinrådets vurderingsrapport sammenlignes med prednisolon og deflazacort. Nedenstående tabel 2 viser de årlige lægemiddeludgifter for henholdsvis Agamree, Prenisolon samt Deflazacort.

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient

Lægemiddel	Styrke (pakningsstørrelse)	Dosering*	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Agamree	40 mg/ml (100 ml oral suspension)	6 mg/kg/dag	[redacted]	[redacted]
Prednisolon "DAK"	25 mg (100 stk. tabletter)	0,75 mg/kg/dag	[redacted]	[redacted]
Deflazacort "XGX Pharma"	6 mg (60 stk. tabletter)	0,90 mg/kg/dag	[redacted]	[redacted]

*Det antages, at gennemsnitsvægten er 19 kg som i VISION-DMD-studiet jævnfør Medicinrådets vurderingsrapport.

Status fra andre lande

Tabel 3: Status fra andre lande

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

Opsummering

[redacted]

Application for the assessment of AGAMREE® for the treatment of Duchenne muscular dystrophy in patients aged 4 years and older

Color scheme for text highlighting	
Color of highlighted text	**Definition of highlighted text**
	Confidential information

Contact information

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Tables and Figures

Abbreviations

6MWT	6 Minute Walk Test
AE	Adverse event
ADHD	Attention-deficit/hyperactivity disorder
AESI	Adverse event of special interest
AIP	Pharmacy wholesale price
AL	Aluminium
ATC	Anatomical Therapeutic Chemical
BMD	Bone mineral density
BMI	Body mass index
CDC	Centers for Disease Control and Prevention
CINRG	Cooperative International Neuromuscular Research Group
CI	Confidence interval
CEAC	Cost-effectiveness acceptability curve
cm	Centimetres
DMC	Danish Medicines Council
DMD	Duchenne muscular dystrophy
DKK	Danish krona
DNHS	Duchenne Natural History Study
DEXA	Dual-energy X-ray absorptiometry
EAP	Expanded access protocol
EMA	European Medicines Agency
EQ-5D-3L	EuroQoL five-dimension questionnaire (3 levels)
FVC	Forced vital capacity
HCRU	Healthcare resource use
HDPE	High-Density Polyethylene
HRQoL	Health-related quality of life
HTA	Health technology assessment
HTMF	Hand-to-mouth function
ICER	Incremental cost-effectiveness ratio
ICEP	Incremental cost-effectiveness plane
mITT	Modified Intent-to-treat
IQ	Intelligence quotient
KM	Kaplan-Meier
LSM	Least square mean

LDPE	Low-Density Polyethylene
MCID	Minimal clinically important differences
m	Meter
mg	Milligram
ml	Milligram
MMRM	Mixed Model for Repeated Measurements
MAR	Missing at random
N/A	Not applicable
NHM	Natural history model
NICE	National Institute for Health and Care Excellence
NSAA	North Star Ambulatory Assessment
kg	Kilogram
P1NP	Procollagen type 1 N-terminal propeptide
PARS III	Psychosocial Adjustment and Role Skills Scale III
PROM	Patient-reported outcome measure
PVC	Polyvinyl chloride
REML	Restricted maximum likelihood
QoL	Quality of life
QALY	Quality-adjusted life year
s	Second
SAE	Serious adverse event
CTX	C-terminal telopeptide of type 1 collagen
SE	Standard error
SEM	Standard error of the mean
SOC	System organ class
TEAE	treatment-emergent adverse event
TTRF	Time taken to rise from the floor
TTCLIMB	Time to climb 4 steps
TTRW	Time to Run/Walk 10 meters
TTSTAND	Time to Stand Test
UK	United Kingdom
USA	United States of America
VISION-DMD	VBP15-004

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	AGAMREE®
Generic name	Vamorolone
Therapeutic indication as defined by EMA	Treatment of Duchenne muscular dystrophy (DMD) in patients aged 4 years and older [1]
Marketing authorization holder in Denmark	Santhera Pharmaceuticals (Deutschland) GmbH [2]
ATC code	H02AB18 [2]
Combination therapy and/or co-medication	No
(Expected) Date of EC approval	2023-12-14 [2]
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	Yes (22 August 2014) [2]
Other therapeutic indications approved by EMA	No
Other indications that have been evaluated by the DMC (yes/no)	No
Joint Nordic assessment (JNHB)	No, the treatment is not suitable for a Joint Nordic assessment since there may be differences in treatment practices across the Nordic countries. For instance, deflazacort (a glucocorticoid used to treat DMD) is not reimbursed in all Nordic countries and there may be differences in the dosing of glucocorticoid therapy. A survey in Europe and USA has shown that 29 different regimens of glucocorticoids are used [3]. For example, 10 days on/10 days off [3], 10 days/month [4], and weekend dosing at 5 mg/kg [3].
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	Each pack contains one glass bottle (containing 100 ml oral suspension of vamorolone 40 mg/ml), one press-in bottle adapter (low density polyethylene) and two identical oral syringes (low density polyethylene) [1]

Abbreviations: ATC = Anatomical Therapeutic Chemical DMD = Duchenne muscular dystrophy; mg = milligram; ml = milliliter; kg = kilogram.

2. Summary table

Summary	
Indication relevant for the assessment	Treatment of Duchenne muscular dystrophy (DMD) in patients aged 4 years and older.
Dosage regiment and administration	Oral administration. The recommended dose is 6 mg/kg once daily in patients weighing less than 40 kg. In patients weighing 40 kg and above, the recommended dose of vamorolone is 240 mg (equivalent to 6 ml) once daily [1].
Choice of comparator	Glucocorticoid treatment (prednisone/prednisolone[a] and deflazacort).
Prognosis with current treatment (comparator)	Glucocorticoid therapy has demonstrated benefit in both ambulatory and non-ambulatory DMD patients [5-9]. However, the use of glucocorticoids in DMD patients is associated with potentially serious adverse effects [10] such as growth stunting, osteoporosis, and increased risk of fractures [11], as well as severe mood swings and psychological effects [12, 13], which often lead to dose reductions or stopping the treatment [3, 5, 14], with resulting loss of efficacy [5, 15, 16].
Type of evidence for the clinical evaluation	Head-to-head comparison of vamorolone versus prednisone[a] in VISION-DMD (VBP15-004) and matched comparison of vamorolone versus prednisone and deflazacort in FOR-DMD.
Most important efficacy endpoints (Difference/gain compared to comparator)	As clinically relevant improvement in safety parameters is the advantage of vamorolone compared to current glucocorticoid treatment, key safety endpoints are also included below. VISION-DMD (VBP15-004) TTSTAND velocity: Vamorolone 6 mg/kg demonstrated no statistically significant difference to the recommended dose of prednisone 0.75mg/kg/day in TTSTAND velocity at Week 24. Safety endpoints: Vamorolone 6 mg/kg was well-tolerated during 48 weeks of treatment. Compared with prednisone, there were clinically relevant improvements in the safety outcomes with respect to growth, bone biomarkers and behavioural problems [17, 18]. This is described in section 9.1.1. Matched comparison of VISION-DMD and FOR-DMD TTSTAND velocity: at month 12, there were no significant differences between vamorolone 6.0 mg/kg/day and the recommended dose of prednisone 0.75 mg/kg/day or deflazacort 0.90 mg/kg/day. Safety: vamorolone demonstrated positive height increase at Month 6 and 12 whereas stunting of growth was observed in prednisone and deflazacort (section 9.1.2).

Summary	
Most important serious adverse events for the intervention and comparator	VISION-DMD, Period 1 (24 week): no serious adverse events for vamorolone, prednisone or placebo; Period 2 (Week 28 + 1 day to Week 48): 1 patient in the vamorolone arm had a perforated appendicitis and 1 patient developed asthma.
Impact on health-related quality of life	Clinical documentation: HRQoL was based on the literature. Health economic model: Vamorolone leads to better HRQoL outcomes versus prednisolone and deflazacort.
Type of economic analysis that is submitted	Cost-utility analysis with a cohort-based Markov natural history model.
Data sources used to model the clinical effects	Clinical effect is assumed similar for vamorolone and prednisolone and deflazacort. Transitions between health are derived from a Natural History Model (section 8.2).
Data sources used to model the health-related quality of life	Both health state utilities and adverse event disutilities are derived from literature.
Life years gained	Vs prednisolone: [redacted]; Vs deflazacort: [redacted]
QALYs gained	Vs prednisolone: [redacted]; Vs deflazacort: [redacted]
Incremental costs	Vs prednisolone: [redacted]; Vs deflazacort: [redacted]
ICER (DKK/QALY)	Vs prednisolone: [redacted]; Vs deflazacort: [redacted]
Uncertainty associated with the ICER estimate	[redacted]
Number of eligible patients in Denmark	[redacted]
Budget impact (in year 5)	[redacted]

Note: [a] Prednisone is a synthetic anti-inflammatory glucocorticoid that is converted to prednisolone in the liver [19]. Doses are equivalent for prednisolone and prednisone. Prednisone was used in clinical trials (VISION-DMD, FOR-DMD) presented in this application. In Danish clinical practice, prednisolone is used for the treatment of DMD. In this application those substances refer to the same treatment and are used interchangeably. Abbreviations: mg = milligram; ml = milliliter; kg = kilogram; DKK = Danish krona; CI = confidence interval; LSM = Least square means; ICER = incremental cost-effectiveness ratio; QALY = quality adjusted life years; SE = standard error; TEAEs = treatment emergent adverse events; TTSTAND = Time to stand test.

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

3.1 The medical condition

Duchenne muscular dystrophy (DMD) is a rare, inherited, multi-systemic and progressive disease. The disease is linked to the X-chromosome; therefore, it almost exclusively affects males. DMD is caused by mutations of the dystrophin gene, which codes for the dystrophin protein. Dystrophin provides structural stability to the dystrophin-associated glycoprotein complex on muscle cell membranes. The lack of dystrophin results in membrane fragility, necrosis, inflammation, and transformation of muscle tissue into scar and fat tissue, leading to progressive muscle atrophy and muscle weakness in the lower and upper body [20].

The diagnosis of DMD is based on symptoms, clinical exam, biopsy, and genetic testing for confirmation. A blood test for creatine kinase is the first step in the diagnostic process. Genetic testing detects large changes in the gene (deletion or duplication of whole exons). Next generation sequencing looks at the letters of the code that spell out the instructions for making dystrophin that are found within the DMD gene [10]. Diagnosis usually proceeds as depicted in Figure 26 in Appendix M.

DMD progresses through 5 defined stages ultimately leading to early death: presymptomatic stage, early ambulatory stage, late ambulatory stage, early non-ambulatory stage and late non-ambulatory stage. Major milestones in the disease progression are the loss of ambulation, the loss of self-feeding and the start of night-time assisted ventilation followed by daytime ventilation [21, 22]. The natural course of DMD leads to loss of independent ambulation typically before age of 15, declining pulmonary function due to increasing respiratory muscle weakness, loss of upper limb and hand function, scoliosis, and chest wall abnormalities. Muscle loss first starts to be noticed in childhood and affects the muscle strength, muscle function, and flexibility in the hips, thighs, shoulders, and pelvis. Muscle weakness is compounded by increased risk of bone fragility and the adverse demineralizing effects of long-term use of glucocorticoids add in resulting in low-trauma long-bone and vertebral fractures [23]. As muscle weakness progresses, the patient requires assistance with activities of daily living, such as feeding, washing, toileting, breathing, moving into bed, turning at night etc. by the late teens or in their early twenties. Moreover, there is a decline in respiratory function. Patients, usually in their teens, will require ventilation at night initially and then eventually during the day [24-27].

In Denmark, a registry study between the years 1994 – 2021 showed that wheelchair dependency and respiratory dependency increased in DMD patients as the disease

progressed [28]. Wheelchair dependency increased from <5% in patients aged 0 to 7 years, to 17% in patients aged 8 to 11, 49% in those aged 12 to 17, and 88% in the age group 18 years and above [28]. Respiratory dependency increased from <5% from patients aged 0 to 11 years, to 22% in those aged 12 to 17 years and 78% in patients aged 18 and older [28].

Muscle weakness, bone-related comorbidities [28], cardiovascular complications and respiratory failure cause the most significant burden of illness in patients with DMD mortality [22, 29, 30]. The high disease burden is associated with great health care resource use. A Danish registry-based study revealed that individuals with DMD aged >12 years, 39% and 59% were diagnosed with scoliosis or heart disease, respectively. Of the studied DMD population, 35% underwent Achilles tendon surgery before turning 18 years old, and 86% of DMD individuals aged >8 years experienced respiratory failure. Mean age at first respiratory mask treatment was 15.3 years and 141 of 213 DMD patients were receiving this treatment. At-home mechanical respirator treatment was started, on average, at age 23.2 and being used by 127 of the 213 studied DMD patients [28].

Cardiovascular complications and respiratory failure are key contributors to mortality [22] [29, 30]. The mean age at death of Danish DMD patients is 26.8 years (interquartile range 19 – 34) [28]. DMD patients have a 23.3 times higher risk of death compared with the general Danish population [28].

During 20 years following DMD diagnosis (between the years 1994 – 2021), the total extra direct costs in Denmark per patient amounted to EUR 221,500 for inpatient care, EUR 37,600 for outpatient care, EUR 15,000 for primary care, and EUR 6,400 in prescription drug costs and EUR 32,500 in home care costs [28]. The costs for inpatient care are driven by the extra cost of non-invasive ventilation and in-home mechanical respiration. Furthermore, those costs are observed to increase with the increasing age of the patient [28].

Overall, DMD severely impairs patients' quality of life. A Danish study revealed that the average adult DMD patient depends on mechanical ventilation, has very limited mobility, low level of education, rarely gets a job and almost never starts a family. A great proportion of surveyed patients reported experiencing severe pain daily (38.5%), and limited capability to perform daily activities due to fatigue (52.4%). Moreover, most of those patients have a 24-hour care system [31].

Finally, individuals with DMD are at an increased risk of disordered mental development, behavioural and emotional difficulties. Those behavioural challenges are exacerbated by significant side effects of glucocorticoid treatment that include changes in behaviour (irritability, hyperactivity, euphoria, mood lability, depression) [32, 33]. DMD patients typically have an intelligence quotient (IQ) lower than that of the general population; 27% of them have an IQ below 70. Other common disorders include attention deficit hyperactivity disorder (ADHD), learning difficulties, speech disorders (including delayed language development), autism spectrum, obsessive-compulsive disorder and anxiety [34].

3.2 Patient population

The patient population relevant for this assessment is based on the approved indication of vamorolone - DMD patients aged 4 years and older [1]. In Denmark, patients are usually diagnosed with DMD at the age of 4, this is also when the treatment is initiated [35]. The majority of patients are male (fewer than five are female) [33]. The weight of Danish patients is generally the same as for other boys in same age group [35], however, the boys are usually shorter compared to their healthy peers [35].

The incidence and prevalence in Denmark for the past 5 years is based on a recent Danish study and estimates, presented in Table 1 [28]. Patients were included if they were observed with a DMD diagnosis in a hospital on at least two occasions [28].

Prevalence numbers in the coming five years were assumed [redacted]. It was estimated that [redacted] of prevalent patients were eligible for treatment (Table 2) as most patients in Denmark today are treated with glucocorticoids.

Table 1 Incidence and prevalence in the past 5 years

Year	2020	2021	2022	2023	2024
Incidence in Denmark [28]	7	8	7	7	7
Prevalence in Denmark [28]	164	172	176	178	180
Global prevalence [36]	2.8/100 000 in the general population and 19.8/100 000 live male births				

Note: Data available until year 2021 for incidence and 2020 for prevalence. Values from 2022 onwards are based on estimates.

Table 2 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	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

3.3 Current treatment options

Standard of care for DMD patients in Denmark

There is no cure for DMD, therefore the treatment goal is to start supportive treatment early and to slow disease progression for as long as possible [37]. To manage disease symptoms, individuals with DMD require multidisciplinary patient-centred care (e.g., specialist doctors, nurses, physio- and speech therapists, dieticians, respiratory care staff, home care assistance) [28]. There are currently no Danish treatment guidelines for DMD [38], however, international guidelines exist [10, 22, 39, 40]. According to Danish clinical expert [35], treatment of DMD in Denmark is in line with international guidelines [10]. The

first international treatment guideline was published in 2010 [39] and has been updated in 2018 [10, 22, 40]. International treatment guidelines recommend physiotherapy and treatment with glucocorticoids for DMD, both of which should be continued after loss of ambulation [10].
It is recommended to initiate glucocorticoids early before substantial physical decline, and after a discussion of side-effects [10]. Glucocorticoid therapy has demonstrated benefit in both ambulatory and non-ambulatory patients [5-9]. Glucocorticoid therapy is associated with a delay in the loss of mobility, upper limb function [6, 8], pulmonary function [7, 8], cardiac function [8] and need for scoliosis surgery and ventilation [9]. Long-term (>1 year) treatment has shown a benefit compared with <1 month treatment or no treatment across the lifespan of DMD patients [6, 7].

Glucocorticoid therapy includes prednisone/prednisolone and deflazacort in the recommended starting doses of 0.75 mg/kg/day for prednisone/prednisolone and 0.90 mg/kg/day for deflazacort (see Figure 1) [10]. A double-blind randomised 3-year clinical trial applying either of the recommended daily doses and a lower intermittent prednisone dose, showed that the two daily regimens after 3 years resulted in significant improvement in the composite outcome of motor function, pulmonary function and treatment satisfaction, compared to the intermittent dosing, and with no significant differences between daily prednisone and daily deflazacort [5].

In Europe, prednisolone is typically used instead of prednisone [39]. This is also true for Denmark, according to Danish clinical input [35]. Glucocorticoid therapy is the standard of care for the treatment of DMD in Denmark according to clinicians from Aarhus University Hospital [31], Amgros [41] and DMC [38]. DMC has previously assessed that the majority of DMD patients receive glucocorticoid treatment [38]. According to Danish clinical input, deflazacort and prednisolone are used in the treatment of DMD in Denmark [35]. Both deflazacort and prednisolone have general reimbursement in Denmark [42].

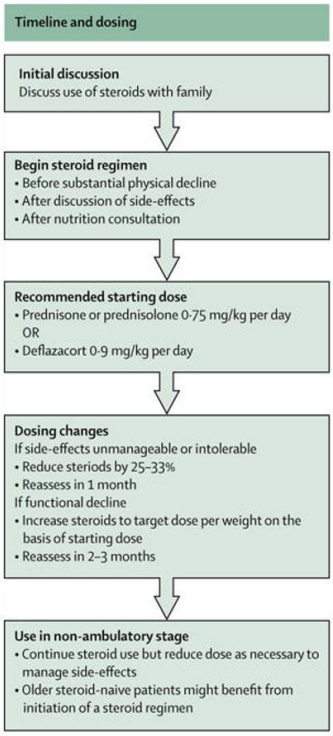
A Danish clinical expert has described that all DMD patients are offered glucocorticoids and that patients generally continue treatment until non-tolerance or death [35]. In Danish clinical practice, until recently, treatment typically was started with daily prednisolone and patients were later often switched to daily deflazacort due to concerns over side effects of prednisolone [35].

There are local differences in the way glucocorticoids are administered in Denmark [redacted]

The 10-day on/10-day off prednisolone treatment has been shown to be less effective in prolonging the time to progression [5]. Daily dosing was found to prolong the time to loss

of ambulation by two [43] to four [44] years compared to intermittent dosing (10 days on/ 10 days off).

Figure 1 International guideline on glucocorticoid initiation



Abbreviations: mg = milligram; kg = kilogram. Source: [10]

Adverse effects of prednisolone and deflazacort

Despite the benefits of glucocorticoid therapy in DMD treatment, the 2018 treatment guidelines caution that prednisone/prednisolone and deflazacort are associated with potentially serious adverse effects such as growth stunting, osteoporosis, increased risk of fractures and developing cataracts, and severe mood swings and psychological effects [11],[39],[40],[45]. Recommendations have been published on dose reduction [10] and are presented in Figure 1.

Stunted growth

While both prednisone/prednisolone and deflazacort are known to negatively affect growth, multiple studies have shown treatment with daily deflazacort to have the most detrimental effect on growth (i.e., growth delay, stunting), more so than prednisone/prednisolone [4, 5, 23, 46]. Findings from the Cooperative International Neuromuscular Research Group Duchenne Natural History Study (DNHS) showed that patients on deflazacort had higher incidence of growth delay than those on prednisone (60% vs 27%, p = 0.0001).

Fractures

It was found that fragility fractures are commonly reported in glucocorticoid treated boys with DMD, the highest fracture incidence rate was observed in those treated with daily deflazacort at 1367 per 10 000 person-years (95% CI, 796-2188) [46]. In daily prednisolone group the incidence rate was 748 per 10,000 person-years, and for the intermittent

treatment regiments the rates were 577 and 512 per 10,000 person-years for deflazacort and prednisolone, respectively [46].

Cataracts

Cataracts are a common side effect of glucocorticoid treatment of DMD patients, especially treatment with deflazacort [3, 16, 46]. A retrospective review of 596 DMD patients found the prevalence of cataracts to be 22.4% among 514 patients receiving corticosteroids [46].

Behavioural changes

Behavioural abnormalities, such as aggression and irritability, are commonly associated with chronic corticosteroid treatment, i.e. prednisone and deflazacort, in patients with DMD and may necessitate a change in treatment [3]. In the FOR-DMD trial the most common adverse events (AEs) (34%) in DMD patients treated with the recommended daily prednisone dose of 0.75mg/kg was abnormal behaviour, which was even more common (38%) in the daily 0.90 mg/kg deflazacort-treated patients [5].

Weight gain

In terms of weight gain, no significant difference was found between the daily prednisone and intermittent prednisone regimens [5]. Patients treated with both prednisone regimens gained more weight than participants receiving deflazacort 0.90 mg/kg/day. The between-group difference in weight gain at month 36 was 2.6 kg (98.3% CI, 0.2 to 5.0 kg) for daily prednisone vs daily deflazacort (P = .01) and −3.1 kg (98.3% CI, −5.5 to −0.7 kg) for daily deflazacort vs intermittent prednisone (P = .002). Furthermore, weight gain was one of the main reasons for dose reductions [5].

Dose reductions

Concerns over AEs of glucocorticoids have led to parents deciding to not initiate treatment, both in Denmark [38] and in Norway [47]. In Norway, 22% of DMD patients were not started on glucocorticoids [47]. While 78% of Norwegian patients received glucocorticoids, the average daily dose for prednisolone and deflazacort used was below the recommended dosage due to concerns over AEs; moreover, a 9% discontinuation rate due to unacceptable side effects was reported, despite patients being on suboptimal dosing (on average) [47].

Internationally, concerns over AEs have led to lower doses (on average 67% of recommended dose) [14, 47], and intermittent dosing [3, 4]. A survey in Europe and USA has shown that 29 different dosing regimens are used [3]. For example, intermittent regimes such as 10 days on/10 days off [3], 10 days/month [4], and weekend dosing at 5 mg/kg [3] have been reported.

Several studies have demonstrated that sub-optimal doses from down-titrating glucocorticoids by reducing the daily dose or using intermittent dosing leads to loss of efficacy [5, 15, 16]. Two studies have concluded that daily glucocorticoid dosing resulted in better efficacy versus intermittent dosing when it comes to the median age at loss of ambulation [15, 16]. Moreover, a randomised clinical trial confirmed that daily glucocorticoid dosing had significant benefit over intermittent dosing in a composite

outcome measure of motor function, pulmonary function, and satisfaction with treatment over a 3-year period [5]. Either daily or intermittent (10 days on and 10 days off) prednisone regimens were associated with significantly greater weight gain than daily 0.90 mg/kg of deflazacort. Both daily regimens led to stunting of growth, more so with daily deflazacort [5].

Unmet need with current treatment options

Currently there is no cure for DMD and limited treatment options (i.e., prednisolone, deflazacort, symptomatic care). Glucocorticoids are associated with significant adverse effects that reduce patient and care giver quality of life and often result in ineffective dosing or treatment discontinuation. Given the lack of treatments that can be used for all patients irrespective of stage of ambulation, or the gene mutation, and the adverse effects associated with glucocorticoids [48], there remains a significant unmet need for all people with DMD. Therefore, it is evident that the current unmet medical need could be addressed by a drug that provides equal or better efficacy than glucocorticoids, but with significantly less adverse effects than prednisone/ prednisolone and deflazacort, such as vamorolone.

3.4 The intervention

Vamorolone is indicated for treating DMD in patients from 4 years of age and was granted marketing authorisation by the European Commission in December 2023 [2]. An overview of vamorolone is presented in Table 3 [1].

Vamorolone is a dissociative corticosteroid that selectively binds to the glucocorticoid receptor, which triggers anti-inflammatory effects via inhibition of nuclear factor-kappa B mediated gene transcripts, but leads to less transcriptional activation of other genes [1]. In addition, vamorolone inhibits the activation of the mineralocorticoid receptor by aldosterone. Due to its specific structure, vamorolone is likely not a substrate for 11ß-hydroxysteroid dehydrogenases and is therefore not subject to local tissue amplification [1].

Table 3 Overview of vamorolone

Overview of intervention	
Indication relevant for the assessment	Treatment of DMD in patients aged 4 years and older.
ATMP	No
Method of administration	Oral
Dosing	6mg/kg once daily in patients weighing less than 40 kg; 240 mg (equivalent to 6 ml) once daily in patients weighing 40 kg and above; daily dose may be down-titrated to 4 mg/kg/day or 2 mg/kg/day based on individual tolerability.

Overview of intervention	
Dosing in the health economic model (including relative dose intensity)	Patients receive 6mg/kg once daily as a starting dose. Thereafter, 10% of patients down-titrate to 4mg/kg after 6 months based on evidence from VISION-DMD where the occurrence of treatment emergent adverse events (TEAEs) during the 12-month period was low.
Should the medicine be administered with other medicines?	No medicine needs to be co-administered during the administration of vamorolone.
Treatment duration / criteria for end of treatment	Patients are treated until they discontinue due to lack of tolerance to intervention, or else until death.
Necessary monitoring, both during administration and during the treatment period	Close treatment monitoring is recommended for patients who have diabetes mellitus, increased risk of infections, glaucoma, altered thyroid function, adrenal insufficiency and disease / history of thromboembolic events.
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	After diagnosis of DMD, no additional diagnostic testing is needed for treatment and is therefore not included in the model.
Package size(s)	Each pack contains one glass bottle (containing 100 ml oral suspension of vamorolone 40 mg/ml), one press-in bottle adapter (low density polyethylene) and two identical oral syringes (low density polyethylene) [1]

Abbreviations: mg = milligram; ml = milliliter; kg = kilogram.

3.4.1 The intervention in relation to Danish clinical practice

In Danish clinical practice both prednisolone and deflazacort are used. All DMD patients are offered glucocorticoids and patients generally continue treatment until non-tolerance or death, which has been confirmed by a Danish clinical expert [35]. Vamorolone is anticipated to be used as an alternative to current glucocorticoid treatment with prednisolone and deflazacort. Consequently, prednisolone and deflazacort are expected to be partially replaced by vamorolone in the management of DMD.

3.5 Choice of comparator(s)

Glucocorticoid therapy is the standard of care for the treatment of DMD in Denmark, according to clinicians from Aarhus University Hospital [31], Amgros [41] and DMC [38]. DMC has previously assessed that the majority of DMD patients receive glucocorticoid treatment [38]. The glucocorticoids prednisolone and deflazacort are the relevant comparators, as they are used in the treatment of DMD in Denmark [31] [35]. An overview of prednisolone and deflazacort is provided in the tables below.

Table 4 Overview of comparator - prednisolone

Overview of comparator - prednisolone	
Generic name	Prednisolone
ATC code	H02AB06 [49-51]
Mechanism of action	Prednisolone is a corticosteroid with glucocorticoid and mineralocorticoid activity. Compared with hydrocortisone, the main anti-inflammatory corticosteroid in humans, it has 4 times greater glucocorticoid potency but lower mineralocorticoid potency [49-51] .
Method of administration	Oral administration via tablets [49-51].
Dosing	Prednisolone does not have an indication specific for DMD [49-51], however, in international guidelines, the recommended starting daily dose for DMD patients is 0.75 mg/kg [39]. Based on the tolerance to side effects, guidelines on dose reductions are available, as shown in Figure 1 [10].
Dosing in the health economic model (including relative dose intensity)	Prednisolone patients receive 0.75mg/kg as a starting dose in the model. Patients down-titrate to an average of 0.35mg/kg, which is calculated based on the average dose patients received by age in the CINRG dataset.
Should the medicine be administered with other medicines?	No medicine needs to be co-administered during the administration of prednisolone.
Treatment duration/ criteria for end of treatment	Treatment with prednisolone is chronic and recommended for ambulatory and non-ambulatory patients [10, 39]. If side-effects are unmanageable and/or intolerable, at least one dose reduction or alternative dosing regimen should be pursued. If side effects are still not manageable and tolerable, then the treatment should be discontinued regardless of the state of motor function [10].
Need for diagnostics or other tests (i.e. companion diagnostics)	After DMD diagnosis, no additional diagnostic testing is needed for treatment and is thus not included in the model.
Package size(s)	Prednisolone “EQL Pharma”: HDPE tablet container with LDPE/HDPE lid [49]; 2.5 mg: available in packs containing 100 tablets; 5 mg: available in packs 25, 100 and 300 tablets; 25 mg: available in packs containing 10 and 100 tablets; Prednisolone “DAK”: Glass tablet container [50]; 5 mg: available in packs containing 100 tablets; 25 mg: available in packs containing 10 and 100 tablets; Prednisolone “Actavis”a: AL/PVC blister pack [51]; 25 mg: available in packs containing 10 and 100 tablets

[a] Only packs marketed in Denmark according to medicinpriser.dk are shown (as of 11 February 2025)
Abbreviations: ATC = Anatomical Therapeutic Chemical; AL = aluminium (foil); HDPE = High-Density Polyethylene; LDPE = Low-Density Polyethylene; N/A = not applicable; PVC = polyvinyl chloride; mg = milligram; kg = kilogram.

Table 5 Overview of comparator - deflazacort

Overview of comparator - deflazacort	
Generic name	Deflazacort
ATC code	H02AB13 [52]
Mechanism of action	Deflazacort is a synthetic glucocorticoid with anti-inflammatory properties similar to other corticosteroids [52].
Method of administration	Oral administration via tablets [52].
Dosing	For DMD patients aged 2 years and above, the recommended starting daily dose is dose is 0.90 mg/kg [39, 52]. Based on the tolerance to side effects, guidelines on dose reductions are available, as shown in in Figure 1 [10].
Dosing in the health economic model (including relative dose intensity)	Deflazacort patients receive 0.75mg/kg as a starting dose in the model. Patients down-titrate to an average of 0.35mg/kg, which is calculated based on the average dose patients received by age in the CINRG dataset.
Should the medicine be administered with other medicines?	No medicine needs to be co-administered during the administration of deflazacort.
Treatment duration/ criteria for end of treatment	Treatment with deflazacort is chronic [39], indicated for DMD patients aged 2 years and above [52], and recommended for ambulatory and non-ambulatory patients [39]. If side-effects are unmanageable and/or intolerable, at least one dose reduction or alternative dosing regimen should be pursued. If side effects are still not manageable and tolerable, then the treatment should be discontinued regardless of the state of motor function [10].
Need for diagnostics or other tests (i.e. companion diagnostics)	After diagnosis of DMD, no additional diagnostic testing is needed for treatment and is therefore not included in the model.
Package size(s)	1 pack contains 60 tablets. Each tablet contains 6 mg of deflazacort [53]

Abbreviations: ATC = Anatomical Therapeutic Chemical; mg = milligram; kg = kilogram.

3.6 Cost-effectiveness of the comparator(s)

The relevant comparator, glucocorticoid therapy has not been previously assessed by DMC. However, according to the methods guide [54], DMC can accept a comparator that has not previously been assessed if certain criteria are met (established standard Danish treatment practice, documented effect on patient population, low costs). As demonstrated in Table 108 in Appendix N, glucocorticoid therapy meets those criteria.

3.7 Relevant efficacy outcomes

Efficacy outcomes are included below. However, clinically relevant improvement in safety parameters is the advantage of vamorolone compared to current glucocorticoid treatment. Thus, please note that safety outcomes on height, bone biomarkers and behavioural problems are relevant for this application, and the results are presented in section 9.1.1 and 9.1.2.

3.7.1 Definition of efficacy outcomes included in the application

The main efficacy outcomes considered relevant to evaluate the effect of the vamorolone versus glucocorticoids is TTSTAND. TTSTAND is an early prognostic factor for disease progression and loss of ambulation [55, 56] and is included in this application for both VISION- and FOR-DMD and defined in Table 6. Table 109 in Appendix O presents additional details on the collection of TTSTAND, as well as some other endpoints from VISION-DMD for which results vs. placebo are presented in this application.

Table 6 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
VISION-DMD			
TTSTAND (Time to stand from supine)	Week 24	TTSTAND is a linear measurement of the number of seconds to rise from a supine position without assistance. TTSTAND velocity was calculated as 1/TTSTAND expressed as rises/second [17, 57]. [redacted]	The change from baseline was calculated from baseline (first study visit) to week 24 (last study visit of the study Period 1).
FOR-DMD			
Rise from the floor velocity	Month 36	Time taken to rise from the floor (TTRF) velocity is equivalent to TTSTAND expressed in rise/seconds. TTRF velocity	TTRF and TTSTAND velocity outcomes are equivalent since FOR-DMD study protocol reported that all timed motor

(TTSTAND velocity)	component was originally specified as time to rise from the floor. This end point was redefined after the conclusion of follow-up but prior to database lock and unblinding to accommodate data from boys who lost the ability to rise from the floor (infinite time but zero velocity) [5].	function tests were conducted according to NS criteria, which clearly state that the child should be supine on the floor [5].

Handling of missing data in VISION-DMD

For premature discontinuation of study treatment, the treatment policy principle was applied (i.e., all available data collected before or after the discontinuation of study treatment was used). If not stated otherwise, the missing data was imputed under the assumption of missing not at random using Copy-Reference imputation. For data that were missing due to the COVID-19 pandemic, a hypothetical scenario "had the pandemic not impacted study procedures" was applied. Missing data recorded as missing due to the COVID-19 pandemic were imputed under the assumption of missing at random (MAR). For data that are missing due to death, a composite strategy was used. In this scenario, the TTSTAND velocity value was imputed as zero for the next visit that would have been scheduled following the death. A similar composite strategy was applied for TTSTAND velocity values that were missing because the test was not conducted due to disease progression.

Handling of missing data in the matched comparison between VISION-DMD and FOR-DMD

In a matched comparison of VISION-DMD and FOR-DMD, the outcome TTSTAND velocity was compared [5]. In the matched population for FOR-DMD, 6 patients were missing pre-treatment TTSTAND without assistance or 6MWT, and therefore they were not included in the matched comparison (Table 18).

4. Health economic analysis

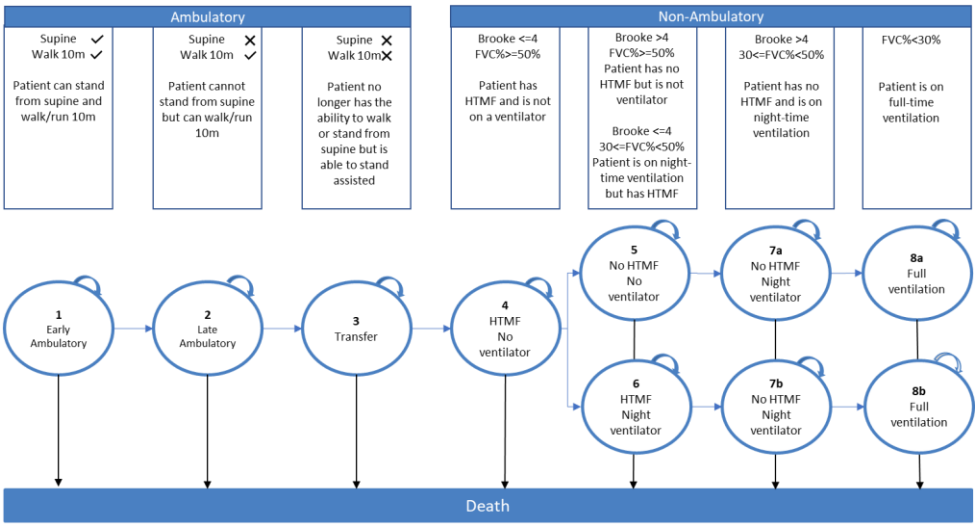
4.1 Model structure

A cohort-based Markov natural history model (NHM) for cost utility analysis was developed in Microsoft® Excel via Project HERCULES [58]. Project HERCULES (HEalth Research Collaboration United in Leading Evidence Synthesis) is a global collaboration set up by Duchenne UK [58]. One of the key outputs from this initiative was the development of a Markov cost-effectiveness model (CEM) [59]. Selection of a Markov model is aligned with the results of the systematic literature review (SLR), which identified six studies, all of which used a Markov structure consistent with the Project HERCULES model.

The process for determining model health states was primarily based on conducting a targeted literature review, performed in MEDLINE which identified existing health state

definitions, key milestones in disease progression, and outcomes captured in clinical trials. The health states were presented for stakeholder input to clinicians, patients and caregivers. The final health states were validated with a group of clinical experts. The model structure is illustrated in Figure 2. The model adopts a multi-state cohort structure, comprising ambulatory and non-ambulatory health states, plus an intermediate 'transfer' health state, and death.

Figure 2 Model schematic



Abbreviations: FVC = forced vital capacity; HTMF = hand-to-mouth function; m = metres

All patients enter the model in health state 1 and progress through the ambulatory states (1 and 2) to the intermediate Transfer health state. After the Transfer state, all patients begin the non-ambulatory state in health state 4 with hand-to-mouth function (HTMF) and the ability to breathe independently. After this point, the cohort of patients splits into one of two pathways (health state 5 or 6), depending on which of these functions is lost first. The distinction between the states 7a and 7b, and 8a and 8b is the route by which the patient cohort reached theses states. Transition probabilities in the model vary according to each pathway; however, the utilities and costs associated with 7a and 7b, and 8a and 8b are the same. Table 7 and Table 8 summarised the functional ability in the ambulatory and non-ambulatory states respectively.

Table 7 Definition of functional ability: ambulatory and transfer health states

Ambulatory status	Ambulatory		Transfer
Sub-states	**Early ambulatory**	**Late ambulatory**	**-**
Health states	**1**	**2**	**3**
Functional ability	Stand from supine; Walk or run 10 metres; Stand	Walk or run 10 metres: Stand	Stand
Function lost	N/A	Stand from supine	Walk or run 10 metres

Abbreviation: N/A = Not applicable.

Table 8 Definition of functional ability by health state – non-ambulatory states

Ambulatory status	Non-ambulatory				
Sub-states	**HTMF, No Ventilation**	**HTMF, Night Ventilation**	**No HTMF, No Ventilation**	**No HTMF, Night Ventilation**	**Full Ventilation**
Health states	**4**	**5**	**6**	**7a, 7b**	**8a, 8b**
HTMF (Brooke score)	≤4	≤4	>4	>4	>4
Pulmonary function (FVC)	>50%	≥30% and ≤50%	>50%	≥30% and ≤50%	<30%
Description	Ability to self-feed, not on a ventilator	Ability to self-feed and is on night-time ventilation	Unable to self-feed, not on a ventilator	Unable to self-feed and is on night-time ventilation	Full-time ventilation

Abbreviations: FVC = Forced vital capacity; HTMF = Hand-to-mouth function.

4.2 Model features

Table 9 Features of the economic model

Model features	Description	Justification
Patient population	DMD patients aged 4 and above	According to the approved EMA indication [60] and validated by Danish clinical expert [35]. There are no deviations from the patient population described in section 3.2.
Model structure	Cohort-based Markov natural history model for a cost-utility analysis	A Markov model is aligned with the results of the systematic literature review (section 5.3)
Perspective	Limited societal perspective	According to DMC guidelines
Time horizon	Lifetime (50 years)	To capture all health benefits and costs in line with DMC guidelines. Validated by Danish clinical expert [35].
Cycle length	One month	Consistent with the available clinical data in VISION-DMD; one month is deemed granular enough to capture disease progression and the impact of AEs.
Half-cycle correction	Yes	Accounts for uncertainties in the timing of transitions with the cycle period

Model features	Description	Justification
Discount rate	3.5 %	The DMC applies a discount rate of 3.5 % for all years
Intervention	Vamorolone	
Comparator(s)	Prednisolone and deflazacort	According to international treatment guidelines [10]. Validated by Danish clinical expert [35].
Outcomes	No efficacy outcomes were modelled explicitly.	

Abbreviations: AE = adverse event; EMA = European Medicines Agency; DMC = Danish Medicines Council.

5. Overview of literature

5.1 Literature used for the clinical assessment

The clinical SLR was conducted in July 2023 and updated in March 2025. The full details are provided in Appendix H. The aim of this SLR was to identify and gather comprehensive clinical evidence (efficacy, safety, discontinuation and tolerability) about vamolorone for the treatment of DMD in boys aged 4 years and older. In summary, 46 publications were identified, which included 16 unique studies. From these, two studies were used in the local adaptation. The VISION-DMD (VBP15-004 / NCT03439670) study was a phase IIb, randomized, double-blind, parallel group study which assessed the efficacy and safety of vamorolone vs placebo and prednisone in males aged ≥4 to <7 years. The other study, FOR-DMD (NCT01603407), was a randomized, prospective, multicentre, double-blind, study which compared three glucocorticoid regimens in boys aged ≥4 years and < 8 years with DMD, who were glucocorticoid naïve at study entry. The rationale for this is presented in section 6.1. Details of VISION-DMD and FOR-DMD are presented in Table 10 below.

Table 10 Relevant literature included in the assessment of efficacy and safety

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*
Guglieri, M., Clemens, P. R., Perlman, S. J., Smith, E. C., Horrocks, I., Finkel, R. S., Mah, J. K., Deconinck, N., Goemans, N., Haberlova, J., Straub, V., Mengle-Gaw, L. J., Schwartz, B. D., Harper, A. D., Shieh, P. B., De Waele, L., Castro, D., Yang, M. L., Ryan, M. M., McDonald, C. M., … Hoffman, E. P. (2022). Efficacy and Safety of Vamorolone vs Placebo and Prednisone Among Boys With Duchenne Muscular Dystrophy: A Randomized Clinical Trial. JAMA neurology, 79(10), 1005–1014 [17]	VISION-DMD	NCT03439670	Start: 29/06/2018 Completion: 19/08/2021	Vamorolone administered orally at daily doses of 2.0 mg/kg and 6.0 mg/kg. vs Prednisone administered orally at a daily dose of 0.75 mg/kg and Placebo administered orally for boys 4 to younger than 7 years of age with genetically confirmed DMD not previously treated with corticosteroids
Guglieri, M., Bushby, K., McDermott, M. P., Hart, K. A., Tawil, R., Martens, W. B., Herr, B. E., McColl, E., Speed, C., Wilkinson, J., Kirschner, J., King, W. M., Eagle, M., Brown, M. W., Willis, T., Griggs, R. C., FOR-DMD Investigators of the Muscle Study Group, Straub, V., van Ruiten, H., Childs, A. M., … Chang, T. (2022). Effect of Different Corticosteroid Dosing Regimens on Clinical Outcomes in Boys With Duchenne Muscular Dystrophy: A Randomized Clinical Trial. JAMA, 327(15), 1456–1468 [5]	FOR-DMD	NCT01603407	Start: 01/2013 Completion: 11/2019	Prednisone 0.75 mg/kg/day, Intermittent prednisone 0.75 mg/kg/day (10 days on, 10 days off), Deflazacort 0.90 mg/kg/day vs NA for boys aged 4 to 7 years with Duchenne muscular dystrophy who had not previously been treated with corticosteroids

* If there are several publications connected to a trial, include all publications used.

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

The HRQoL SLR was conducted with initial search in 2017, followed by update in 2019, 2023 and March 2025, and the methodology is described in Appendix I. The aim of this SLR was to identify and gather comprehensive HRQoL evidence (including utility, disutility and decrements) for the treatment of patients with DMD and their caregivers. In summary, 50 publications were identified, which included 46 unique studies. The literature used for HRQoL is described 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
Landfeldt E, Alfredsson L, Straub V, et al. Economic Evaluation in Duchenne Muscular Dystrophy: Model Frameworks for Cost-Effectiveness Analysis. Pharmacoeconomics 2017. 35: 249–258. [61]	Health state utilities, caregiver disutilities	Section 10.3
Crossnohere, N.L., et al., Assessing the Appropriateness of the EQ-5D for Duchenne Muscular Dystrophy: A Patient-Centered Study. Med Decis Making, 2021. 41(2): p. 209-221.[62]	Health state utilities	Section 10
Matza L, Chung K, Van Brunt K, et al. Health state utilities for skeletal-related events secondary to bone metastases. Eur J Health Econ 2013. 15: 7–18. [63]	Adverse event disutilities	Section 10.3.4
ICER. Deflazacort, Eteplirsen, and Golodirsen for Duchenne Muscular Dystrophy: Effectiveness and Value. Final Evidence Report. 2019; Available from: https://icer.org/wp-content/uploads/2020/10/ICER_DMD_Evidence-Report_071619.pdf. [64]	Adverse event disutilities	Section 10.3.4
de Kinderen RJ, Wijnen BF, van Breukelen G, Postulart D, Majoie MH, Aldenkamp AP, Evers SM. From clinically relevant outcome measures to quality of life in epilepsy: A time trade-off study. Epilepsy Res. 2016 Sep;125:24-31. doi: 10.1016/j.eplepsyres.2016.05.005. Epub 2016 Jun 11. PMID: 27344139. [65]	Adverse event disutilities	Section 10.3.4
NICE. Metreleptin for treating lipodystrophy [ID861] https://www.nice.org.uk/guidance/hst14/evidence/final-evaluation-determination-committee-papers-pdf-9016371757 [66]	Adverse event disutilities	Section 10.3.4
Sullivan PW, Slejko JF, Sculpher MJ, Ghushchyan V. Catalogue of EQ-5D scores for the United Kingdom. Med Decis Making. 2011 Nov-Dec;31(6):800-4. doi: 10.1177/0272989X11401031. Epub 2011 Mar 21. PMID: 21422468. [67]	Adverse event disutilities	Section 10.3.4

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Hvidberg MF, Petersen KD, Davidsen M, et al. Catalog of EQ-5D-3L Health-Related Quality-of-Life Scores for 199 Chronic Conditions and Health Risks in Denmark. MDM Policy & Practice. 2023;8(1). doi:10.1177/23814683231159023 [68]	Adverse event disutilities	Section 10.3.4
Hagiwara Y, Shiroiwa T, Shimozuma K, et al. 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. [69]	Adverse event disutilities	Section 10.3.4
Doyle S, Lloyd A & Walker M. Health state utility scores in advanced non-small cell lung cancer. Lung Cancer 2008. 62: 374–380. [70]	Adverse event disutilities	Section 10.3.4
Dipnall JF, Rivara FP, Lyons RA, Ameratunga S, Brussoni M, Lecky FE, Bradley C, Beck B, Lyons J, Schneeberg A, Harrison JE, Gabbe BJ. Health-Related Quality of Life (HRQoL) Outcomes Following Injury in Childhood and Adolescence Using EuroQol (EQ-5D) Responses with Pooled Longitudinal Data. Int J Environ Res Public Health. 2021 Sep 27;18(19):10156. doi: 10.3390/ijerph181910156. PMID: 34639458; PMCID: PMC8507627. [71]	Adverse event disutilities	Section 10.3.4
Landfeldt E et al. 2016. Quantifying the burden of caregiving in Duchenne muscular dystrophy. Available at: https://pmc.ncbi.nlm.nih.gov/articles/PMC4859858/pdf/415_2016_Article_8080.pdf [72]	Adverse event disutilities - caregivers	Section 10.3.4
Medicinrådet 2021, Appendiks: Aldersjustering for sundheds-relateret livskvalite. Available at: https://medicinraadet.dk/media/mbtgpjjl/efter-1-januar-2021-appendiks-til-medicinr%C3%A5dets-metodevejledning-aldersjustering-adlegacy.pdf [73]	Health state utilities – age-adjustment	Section 10.3.4

5.3 Literature used for inputs for the health economic model

The SLR for health economic models included Economic Evaluation and Healthcare Cost and Resource Use literature review conducted with initial search in 2017, followed by update in 2019, 2023 and March 2025, and the methodology is described in Appendix J. The aim of this SLR was to identify and gather cost-effectiveness evidence and costs and resource use associated with the management treatment of patients with DMD and their caregivers. In summary, under Economic evaluation 15 publications were identified, which included 13 unique studies; and under Healthcare Cost and Resource Use 112 publications were identified, which included 111 unique studies. The literature used for the health economic model is described in Table 12.

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 E, Alfredsson L, Straub V, et al. Economic Evaluation in Duchenne Muscular Dystrophy: Model Frameworks for Cost-Effectiveness Analysis. Pharmacoeconomics 2017. 35: 249–258. [61]	Health state utilities and costs, caregiver disutilities	Systematic literature review	Section 11.4
ICER. Deflazacort, Eteplirsen, and Golodirsen for Duchenne Muscular Dystrophy: Effectiveness and Value. Final Evidence Report. 2019; Available from: https://icer.org/wp-content/uploads/2020/10/ICER_DMD_Evidence-Report_071619.pdf. [64]	Adverse event disutilities	Systematic literature review	Section 11.4

6. Efficacy

6.1 Efficacy of vamorolone compared to placebo and prednisone for DMD patients in VISION-DMD (VBP15-004) and efficacy of three glucocorticoids regimens in FOR-DMD

6.1.1 Relevant studies

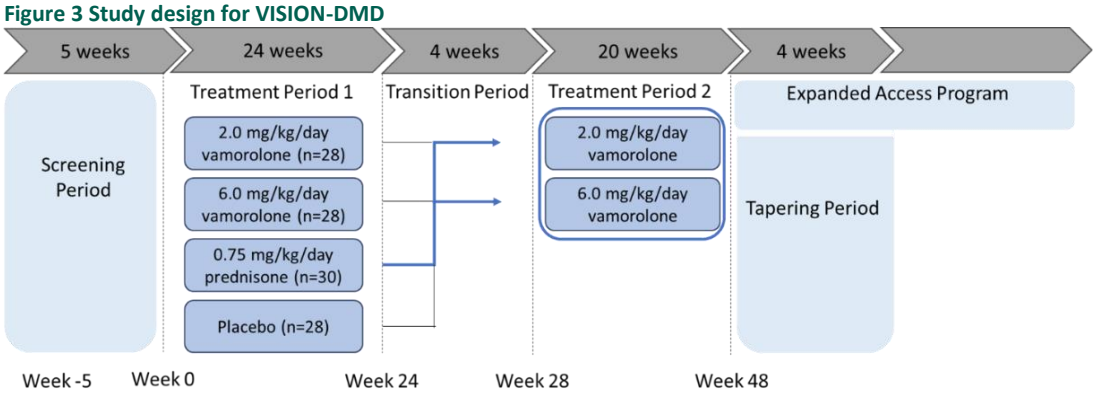
This section focuses on VISION-DMD and FOR-DMD. VISION-DMD is the pivotal trial of vamorolone 2.0 mg/kg/day and 6.0 mg/kg/day versus prednisone over 24 weeks and placebo over 48 weeks. FOR-DMD evaluated the efficacy and safety of glucocorticoid therapy (prednisone and deflazacort) and was used in a matched comparison (described in section 7) of vamorolone versus glucocorticoid therapy. The focus in this application is the vamorolone 6.0 mg/kg once daily dosage, since that is the recommended dose [1].

A brief description of VISION-DMD and FOR-DMD is presented below, with an overview in Table 13 and further information in Appendix A. Note that the information presented for FOR-DMD is based on the relevance to the matched comparison.

VISION-DMD

The VISION-DMD (NCT03439670) study included two sequential 24-week periods [17, 74]. In Period 1, subjects were randomized to 1 of 4 groups: placebo, vamorolone 2.0 mg/kg/day, vamorolone 6.0 mg/kg/day, and prednisone 0.75 mg/kg/day. In Period 2, both placebo- and prednisone-treated subjects crossed over to vamorolone (2.0 mg/kg or 6.0 mg/kg). The overall study design of VISION-DMD is presented in Figure 3.

Figure 3 Study design for VISION-DMD



Abbreviations: mg = milligram; kg = kilogram; n = number of subjects. Source: [75] [74]

The study consisted of the following periods [74]:

- Screening Period (Day -33 to Day -2).
- Baseline Period (Day -1).
- Period 1 (Day 1 to Week 24) to determine if vamorolone treatment led to improvements in strength and mobility compared with placebo treatment and to compare the AE profile for vamorolone with the AE profiles for placebo and prednisone.
- A 4-week Transition Period (Week 25 to Week 28) for subjects who received either placebo or prednisone in Period 1; subjects who received vamorolone in Period 1 were continued on the same dose of vamorolone during this period.

- Period 2 (Week 28 + 1 day to Week 48) in which all subjects received either vamorolone 2.0 mg/kg/day or 6.0 mg/kg/day for 20 weeks to determine if a persistent effect was seen and if there were differences in the safety profile between the vamorolone dose levels with longer treatment.
- Dose Tapering Period (Week 49 to Week 52) in which subjects who elected not to continue vamorolone treatment had the vamorolone dose progressively reduced and discontinued.
- Expanded Access Programmes (EAP): following the completion of Period 2, subjects who elected to continue vamorolone treatment could enter the EAP according to their location.

FOR-DMD

The FOR-DMD (NCT01603407) study was a randomized, prospective, multicentre, double-blind, study to compare three glucocorticoid regimens over a treatment period of 36 to 60 months in boys aged ≥4 years and < 8 years with DMD, who were glucocorticoid naïve at study entry [5]. Patients were randomized as: daily prednisone (0.75 mg/kg/day), intermittent prednisone (0.75 mg/kg/day at 10 days on treatment, 10 days off treatment, and daily deflazacort 0.90 mg/kg/day [5]. All study subjects receive a minimum of 36 months of study medication and up to a maximum of 60 months treatment [5].

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
VISION-DMD, NCT03439670 [17]	Phase IIb, randomized, double-blind, parallel group study on the efficacy and safety of vamorolone vs placebo and prednisone*	48 weeks	n = 121, randomized 2:2:1:1:1:1 and stratified by age at study entry (<6 years and ≥6 years) • Males aged ≥4 to <7 years at enrolment, with a *DMD* gene loss-of-function variation or lack of muscle dystrophin. • Not previously treated with glucocorticoids • Body weight >13.0 kg and ≤39.9 kg at the screening visit. • Able to walk independently without assistive devices. • Able to complete TTSTAND without assistance in <10 seconds at the screening visit.	Vamorolone administered orally at daily doses of 2.0 mg/kg and 6.0 mg/kg.	• Prednisone administered orally at a daily dose of 0.75 mg/kg. • Placebo administered orally.	Efficacy outcomes (the follow-up time was 48 weeks): • TTSTAND velocity (primary endpoint) • TTCLIMB • TTRW • NSAA • 6MWT Safety outcomes (the follow-up time was 48 weeks) • AEs • Height • Bone biomarkers (serum osteocalcin, P1NP and CTX) • Behavioural changes (PARS III) [76]

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
FOR-DMD, NCT01603407 [5]	Phase III, double-blind, parallel group, randomized clinical study on the efficacy and safety of 3 glucocorticoid regimens (daily prednisone, intermittent prednisone and daily deflazacort)	36 months	n = 196 (randomized 1:1:1, stratified by country) • Confirmed diagnosis of DMD defined as: male with clinical signs compatible with DMD and a confirmed DMD mutation in the dystrophin gene. • Age ≥ 4 years and < 8 years. • Ability to rise independently from floor, from supine to standing, as assessed at screening visit. • Ability to maintain reproducible FVC measurements	• Prednisone 0.75 mg/kg/day. • Intermittent prednisone 0.75 mg/kg/day (10 days on, 10 days off). • Deflazacort 0.90 mg/kg/day.	N/A	Efficacy outcomes: • TTRF velocity (equivalent to TTSTAND) • TTRW • NSAA • 6MWT • Safety: • AE • Height All above mentioned outcomes were followed up for 36 months.

*VISION-DMD was prednisone-controlled for the first 24 weeks (of the 48 week study), after which prednisone-treated patients crossed over to the vamorolone arm
Abbreviations: AE = adverse event; CTX = C-terminal telopeptide of type 1 collagen; TTSTAND = Time to Stand Test; TTRF = Time Taken to Rise from the Floor; TTRW = Time to Run/Walk 10 meters; TTCLIMB = Time to climb 4 steps; FVC = Forced vital capacity; 6MWT = 6-minute walk test ; NSAA = North Star Ambulatory Assessment; PARS III = Personal Adjustment and Role Skills Scale, third edition; kg = kilogram; mg = milligram; n = number of subjects. Source: [17] [5]

6.1.2 Comparability of studies

EMA expressed interest in longer-term outcomes of vamorolone versus glucocorticoids beyond the 24 weeks of treatment in VISION-DMD [77]. The external comparison to FOR-DMD has been made to provide additional confirmation of the safety benefits of vamorolone and a similar efficacy profile compared to steroids beyond the 24-week timepoint. When using external data sources, the EMA recommended to pay particular attention to well-matched subject characteristics and assessment protocols, hence the prospective choice of the FOR-DMD study [77].

The FOR-DMD study was an appropriate comparator for the VSION-DMD study because the studies were similar with respect to the following: 1) expertise at the investigational sites (overlapping recruitment sites and study management); 2) daily prednisone dose; 3) treatment duration; 4) subject population; 5) sample size; and 6) harmonization of motor outcome measures and assessment protocols.

There were some differences between VISION-DMD and FOR-DMD. These are described below. In all other aspects, the study designs were considered comparable.

- The FOR-DMD study did not include a placebo control, and all subjects were guaranteed to receive a known effective drug in FOR-DMD. On the other hand, VISION-DMD was placebo-controlled.
- The protocols differed with regard to the level of instructions for prevention (prophylactic measures) and treatment of predictable side effects of corticosteroid medication.
- There was higher frequency of site-patient visits/contact in VISION-DMD (with baseline visit, and following 7 visits in weeks 2, 12, 24, 28, 30, 40 and 48 [17]) than in FOR-DMD, where the baseline visit was performed within 3 months of the screening visit; boys were then evaluated at month 3 and 6, afterwards every 6 months until the end of the study – until the last visit at month 36 – a total of 8 visits [5]).
- VISION-DMD data assessed participants at the 12-, 24- and 48-week timepoints, whereas FOR-DMD included measurements at 6 and 12 months (26 and 52 weeks, respectively).
- There were differences in the timing of the two trials, in some cases differing by several years and including the COVID-19 pandemic in the case of VISION-DMD.
- FOR-DMD was federally funded and run by an academic institution, while VISION-DMD was sponsored by a pharmaceutical company.
- There were differences between the studies with regard to the upper limit of the age range, different criteria for baseline TTSTAND, and difference in upper limit of weight. These have been accounted for the matched comparison described in section 7.1.2. Differences in age range and TTSTAND have been accounted for by matching based on the inclusion criteria. Differences in weight has been accounted for in the calculation of propensity scores.

6.1.2.1 Comparability of patients across studies

Demographic and other baseline characteristics

A matched comparison has been conducted of the vamorolone 2 and 6 mg/kg arms from VISION-DMD versus the prednisone and deflazacort arms in FOR-DMD, as described in section 7.1.2 [78]. As mentioned previously, the focus in this application is the vamorolone 6.0 mg/kg/day once daily dosage, since that is the recommended dose [1].

Table 14 provides a summary of the demographic and baseline characteristics of the population in VISION-DMD and matched subjects in FOR-DMD, based on common inclusion criteria. A full comparison of the baseline characteristics is provided Table 61, Appendix C. The ages were similar for the vamorolone 6 mg/kg group in VISION-DMD and the prednisone and deflazacort groups in FOR-DMD. The geographical distribution for the vamorolone 6.0 mg/kg/day group was similar to that for the matched prednisone group and deflazacort group in FOR-DMD – there is a higher proportion of patients from Europe (>55.4%) and a lower proportion from USA (<44.6%) across all groups. Mean and median height were similar across the groups. Moreover, weight and body mass index (BMI) including the percentiles and z-scores were generally similar across the groups (Table 61, Appendix C).

Table 14 Summary of baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety (VISION-DMD and matched subjects in FOR-DMD)

Variable	VISION-DMD	FOR-DMD	
	Vamorolone 6.0 mg/kg/day (n=28)	Prednisone 0.75 mg/kg/day (n=50)	Deflazacort 0.90 mg/kg/day (n=56)
Age			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]
Region			
Europe	[redacted]	[redacted]	[redacted]
USA	[redacted]	[redacted]	[redacted]
Height (cm)			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]
Weight (kg)			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]

Abbreviations: BMI = body mass index; cm = centimetre; kg = kilogram; max = maximum; min = minimum; m^2 = square metre; mg = milligram; n = number; SD = standard deviation; USA = United States of America. Source: [78]

Table 62 (Appendix C) summarises the baseline assessments for the functional tests TTSTAND velocity for the matched comparison between vamorolone in VISION-DMD versus prednisone and deflazacort in FOR-DMD. Imbalances were noted between the vamorolone groups and the matched prednisone and deflazacort groups, with subjects in the vamorolone groups having worse values at baseline.

Validity of the Matched Comparison for efficacy (TTSTAND)

The validity of the matched comparison for efficacy was investigated by comparing the response to prednisone after 6 months treatment in VISION-DMD and FOR-DMD. There was no significant difference between the prednisone groups across the two studies for TTSTAND velocity, the main efficacy endpoint (Table 63) (Appendix C). In addition, no significant differences were found for the other motor endpoints 6MWT, TTRW or NSAA. Comparison of the efficacy results for vamorolone in VISION-DMD with prednisone in FOR-DMD, support the findings of the VISION-DMD study. Improvements were seen with vamorolone 6.0 mg/kg/day at Weeks 24 and 48 in TTSTAND velocity, which were similar to those seen with prednisone and deflazacort in the FOR-DMD study.

Validity of the matched comparison for height

The baseline data for height in the matched prednisone groups in in VISION-DMD and FOR-DMD are shown in Table 64 (Appendix C). At Baseline, the height was similar in the two prednisone groups, VISION-DMD and matched FOR-DMD, however the percentile height and height z-score were slightly lower for the FOR-DMD prednisone group suggesting a smaller population. The differences are of magnitude similar to the differences across groups seen in the VISION-DMD study, where the prednisone arm presented with the taller children at baseline, suggesting that such differences are in line with the baseline differences that could be seen in height at baseline in a randomized study, so further cross study comparisons are considered valid.

After 6 months, both the prednisone group in VISION-DMD and the matched prednisone group in FOR-DMD had similar changes in absolute height in cm. Considering change in percentile height and height z-score, both groups had decreases consistent with the expected growth stunting, which was were slightly more pronounced in FOR-DMD than VISION-DMD.

Validity of the matched comparison for adverse events

The validity of the cross-study comparison for TEAEs was investigated by comparing the incidence and frequency of TEAEs overall, and by type between the VISION-DMD and FOR-DMD prednisone groups. The incidence of overall TEAEs, the adverse events of special interest (AESIs) and TEAEs leading to discontinuation for the matched VISION-DMD prednisone group and the FOR-DMD prednisone group were similar (Table 65). However, the event rates were higher in the VISION-DMD study than FOR-DMD study, potentially related to differences across the studies such as the higher frequency of visits on site and more frequent laboratory assessments in VISION-DMD, which can all impact the AE reporting-behaviour by parents or investigators for some TEAEs. Therefore, the focus has been on the incidence of TEAEs which may be less affected by differences in visits and/or schedule of assessments.

A higher incidence of clinically relevant TEAEs was observed in VISION-DMD compared with FOR-DMD. As clinically relevant events in both studies were driven by the incidence of the moderate and severe events, the distribution of severity in all events were reviewed (Table 66). The proportions of moderate and severe events were similar in the prednisone groups in each study and therefore a comparison of proportion of events is considered valid for further comparisons. While one event of severe Aggression was reported in the VISION-DMD prednisone group, four severe events were reported in the FOR-DMD prednisone group: Abnormal behaviour, Cushingoid, Weight increased and Influenza. Thus, the pattern of severity and the type of severe events were consistent with what would be expected for this population and for prednisone. The difference in the incidence of clinically relevant events is possibly related to the higher rate of events reported in VISION-DMD, therefore increasing the probability of having at least one moderate or severe event. Therefore, comparisons on incidence of TEAEs by severity was not conducted across studies, but comparison of distribution of severity which uses all events as denominator is considered valid.

A higher incidence of drug-related TEAEs was reported in the prednisone group from the VISION-DMD compared to prednisone in the FOR-DMD study. The reason behind this difference is unclear but may be related to the difference in the approach in an investigational drug study, VISION-DMD, compared to a study with known drugs with an already characterized safety profile.

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

Table 15 focuses on the characteristics that are known to predict DMD diseases progression/severity [78].

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

	Value in Danish population	Value used in health economic model (reference if relevant)
Age at treatment start (years)	4 (based on Danish clinical expert input [35])	4
Gender	Majority male[a] [28]	100% male
Patient weight	Patient weight varies by age	General Danish population 50th percentile weight by ages 2-18+ [79]
Height	N/A	N/A

a Fewer than five female patients have been detected in Denmark [28]

6.1.4 Efficacy – results per VISION-DMD

In the VISION-DMD study, vamorolone 6.0 mg/kg/day demonstrated statistically significant and clinically relevant improvement all five motor function endpoints vs

placebo at week 24: TTSTAND velocity, 6MWT, TTRW, TTCLIMBV and NSAA. These results are presented in Table 57, Appendix B.

Vamorolone 6.0 mg/kg/day demonstrated comparable efficacy to the recommended dose of prednisone 0.75mg/kg/day in TTSTAND velocity at Week 24 – there was no statistically significant difference (Table 16). For participants crossing over from prednisone (Period 1) to vamorolone (Period 2), efficacy was retained for those crossing over to vamorolone 6.0 mg/kg/day (Figure 4). The improvements seen with vamorolone 6.0 mg/kg/day in 6MWT distance, TTRW velocity, TTCLIMB velocity and NSAA score were similar to those seen with prednisone at Week 24, as detailed in **Error! Reference source not found.**.

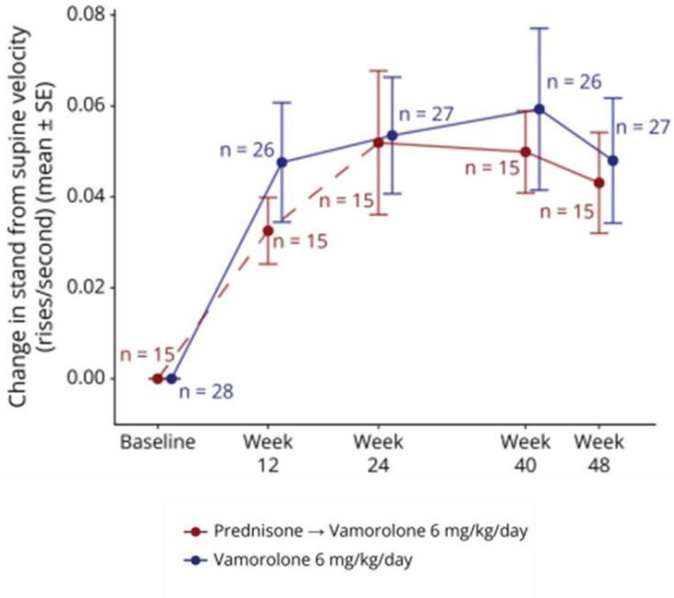
With regard to safety outcomes, vamorolone 6.0 mg/kg/day demonstrated clinically relevant improvements compared with prednisone 0.75 mg/kg/day with respect to growth, bone biomarkers and behavioural problems [17, 18]. This is described in section 9.1.1.

Table 16 Change from baseline to week 24 in TTSTAND velocity – vamorolone 6.0 mg/kg/day vs prednisone 0.75 mg/kg/day (mITT-1 population, VISION-DMD)

TTSTAND Velocity (rises/sec)	Prednisone 0.75 mg/kg/day (N=31)	Vamorolone 6.0 mg/kg/day (N=28)
Change from baseline at Week 24[a]		
N	30	27
Mean (SD)	0.068 (0.0658)	0.054 (0.0666)
Median	0.061	0.041
CI	-0.090, 0.198	-0.082, 0.198
Analysis[b]		
LSE (SE) change from baseline	0.0661 (0.0129)	0.0464 (0.0135)
LSM difference (SE)		-0.0197 (0.0185)
95% CI		-0.0559, 0.0165
p value		0.2865

TSTAND velocity = 1 / TTSTAND and is expressed as rises/sec. Note that velocity was set to 0 for responses determined to be missing due to disease progression (inability to do the test). Moreover, at the first visit a subject could not perform the test due to disease progression, and at ALL subsequent visits, the raw score was left as missing and velocity was imputed as 0.
aDescriptive statistics based on observed cases (without multiple imputation)
bThe LSM estimates are derived from a restricted maximum likelihood (REML)-based MMRM model with multiple imputation based on the missing at random imputation, enrollment stratification age group (4-5 years; 6-<7 years), treatment (vamorolone 2.0 mg/kg/day, vamorolone 6.0 mg/kg/day, prednisone 0.75 mg/kg/day, and placebo), week, baseline response, and the treatment-by-week interaction. Study week was included in the model as a categorical variable (Weeks 6, 12, and 24) along with the treatment-by-week interaction. An unstructured covariance structure was used, and the Kenward-Roger approximation was used to estimate denominator degrees of freedom. Abbreviations: TTSTAND = Time to stand test; N = number of subjects; SD = Standard deviation; SE = Standard error; LSE = Least squares estimation; LSM = Least squares means; CI = Confidence interval.

Figure 4 Change in TTSTAND velocity (rise/sec)



Abbreviations: TTSTAND = Time to Stand Test; SE = Standard error; n = number of subjects, sec = seconds.

6.1.5 Efficacy – results per FOR-DMD

In regard to TTRF velocity, daily prednisone (0.75mg/kg) and daily deflazacort (0.90 mg/kg) demonstrated significant improvement compared with intermittent prednisone regimens. The between-group difference in TTRF velocity was 0.06 rise/s (98.3% CI, 0.03 to 0.08 rise/s) for daily prednisone vs intermittent prednisone (adjusted P = .003), 0.06 rise/s (98.3% CI, 0.03 to 0.09 rise/s) for daily deflazacort vs intermittent prednisone (adjusted P = .017), and −0.004 rise/s (98.3% CI, −0.03 to 0.02 rise/s) for daily prednisone vs daily deflazacort (adjusted P = .75). For more information, refer to Table 59**,** Appendix B.

7. Comparative analyses of efficacy

7.1.1 Differences in definitions of outcomes between studies

The key efficacy outcome in the matched comparison was TTSTAND velocity. In VISION-DMD, TTSTAND was defined as a linear measurement of the number of seconds to rise from a supine position without assistance. TTSTAND velocity was calculated as 1/TTSTAND expressed as rises/second. As explained in section 3.7.1, TTRF investigated in FOR-DMD is equivalent to TTSTAND and thus, only TTSTAND naming is used to describe the outcome of comparative efficacy analyses in this application [5]. Other endpoints compared were 6MWT distance, TTRW velocity and NSAA score.

7.1.2 Method of synthesis

A matched external comparison has been conducted of vamorolone from VISION-DMD (NCT03439670) with prednisone and deflazacort from FOR-DMD (NCT01603407) [78]. The objective was to compare the efficacy and safety of vamorolone administered orally at

daily doses of 2 and 6 mg/kg over a 48-week treatment period in ambulant boys ages 4 to <7 years with DMD in VISION-DMD versus prednisone-treated and deflazacort-treated boys from the FOR-DMD study.

The prespecified efficacy endpoint and safety endpoints (height and treatment emergent adverse events, TEAE) were compared for each vamorolone dose with an external prednisone control group from the FOR-DMD study. Exploratory comparisons for each vamorolone dose with a deflazacort control group from the FOR-DMD study were also conducted. The key comparisons were versus prednisone as VISION-DMD also included a prednisone arm allowing validation of the across study comparisons.

Subject matching for the efficacy comparison

All randomized subjects who had at least one dose of study medication during Treatment Period 2 of VISION-DMD were considered for matching for efficacy. A 2-stage matching approach was used to identify subjects from the FOR-DMD study to include in these analyses. In the first stage, subjects from the FOR-DMD study were matched based on the key inclusion criteria for this study, including confirmed DMD, between 4 and < 7 years of age at Baseline, able to walk independently, and able to complete TTSTAND without assistance.

In the second stage, propensity score matching was conducted. The use of propensity score matching is an established method to estimate the effect of treatment when randomization is not possible and has been used in similar comparisons. One-to-one patient matching was not required, thus allowing for numerically unbalanced sample sizes to retain suitability for cross-study and treatment comparisons [80, 81]. Propensity scores were calculated using a logistic regression model and the following factors that are known to predict DMD disease progression/severity:

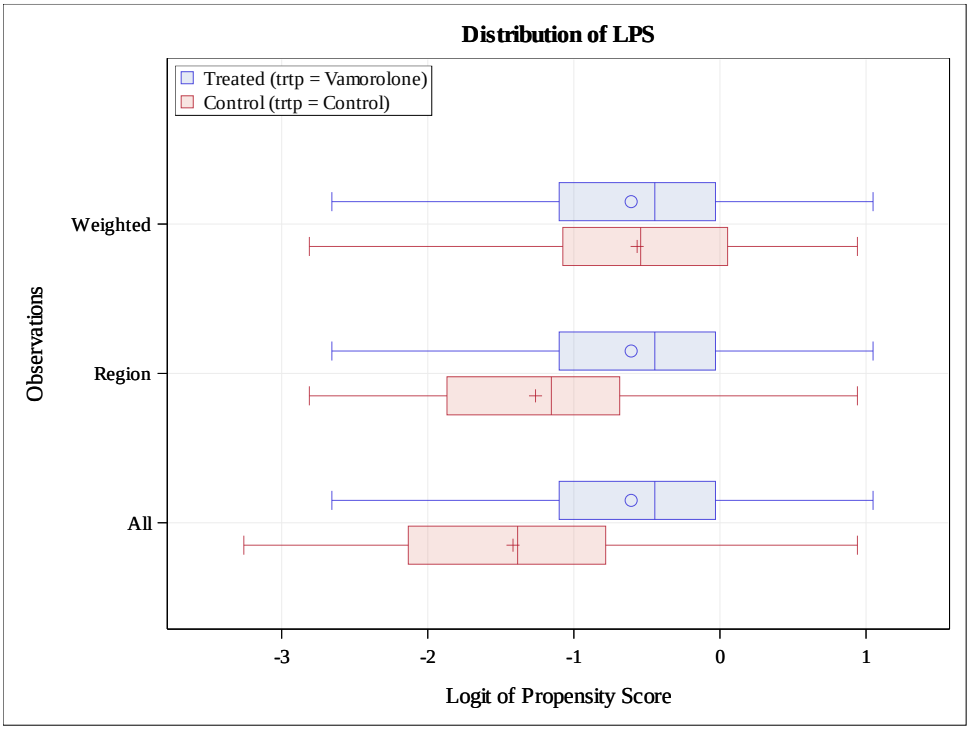
- Baseline age
- Baseline TTSTAND velocity (subjects with baseline TTSTAND > 10 secs were
- excluded)
- Baseline NSAA score
- Baseline weight as z-score
- Baseline height as z-score

The z-score shows the measurement relative to the average of the reference population (e.g., the number of standard deviations away from the average, when the distribution is normal) [82]. For instance, a positive value will be proportionately larger than the average for that age, and a negative value will be smaller than the average for that age.

The dependent variable of the logistic regression model was the outcome that would be observed if the subject received the treatment (1 = treatment, 0 = control). The factors listed above were used as independent variables. All subjects from VISION-DMD meeting the criteria described above (randomized to receive vamorolone throughout 48 weeks) were included in the analyses based on the propensity scores. A common support region was defined based on the propensity score distribution of vamorolone patients. This region identifies the range of propensity scores where both treated and control patients exist, ensuring meaningful comparisons. The common support region was then extended by 0.25 times the pooled estimate of the common standard deviation of the logit of the

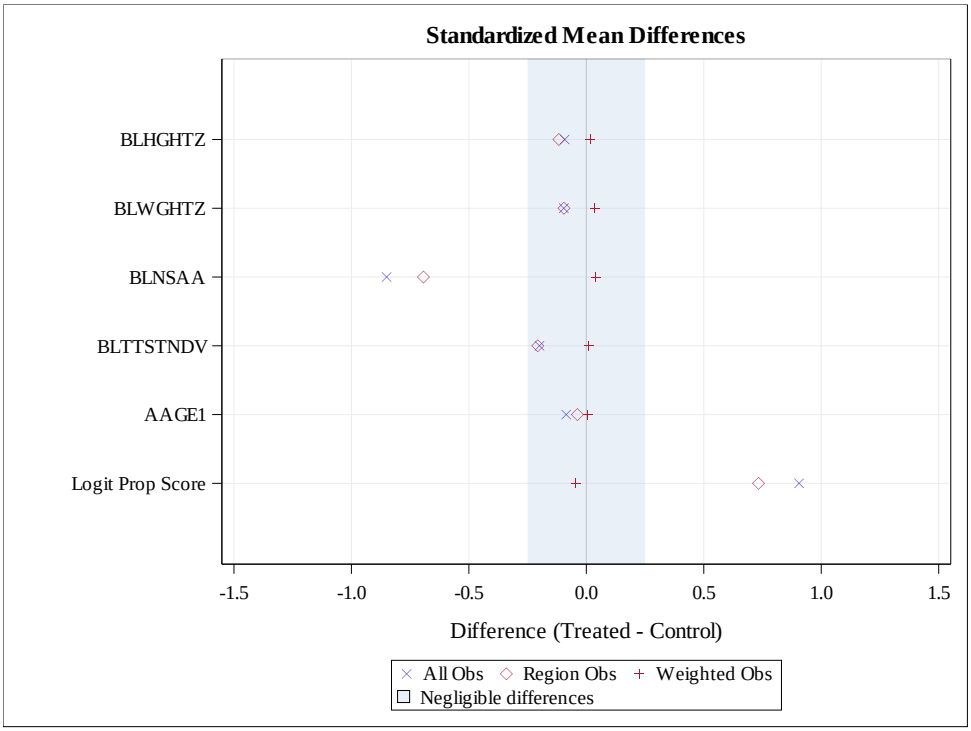
propensity score to include additional control subjects while maintaining adequate overlap. Instead of one-to-one matching between vamorolone and comparator patients, inverse probability weights were assigned to comparator patients. This weighting approach allows all eligible control subjects within the extended common support region to contribute to the analysis, with their contributions reweighted to make the control group resemble the vamorolone group in terms of baseline characteristics. Replacement of the observations from the control dataset was not allowed. The below Figure 5 and Figure 6 show that the weighting balanced the matching parameters between the groups well.

Figure 5, Distribution of logit of propensity score (LPS)



Box: 25%-75%, Line: median, Symbol: mean

Figure 6, Standardized mean differences of measured parameters



BLGHTZ = Baseline weight Z score, BLWGHTZ = Baseline Height Z score, BLNSAA = Baseline NSAA, BLSTTSNDV = Baseline TTSTAND velocity, AAGE1 = Baseline age, Logit Prop Score = Logit propensity score, Obs = Observations

Efficacy Analyses

The comparison of the prespecified efficacy endpoints between vamorolone and prednisone and deflazacort groups at Week 48 focused on a global assessment of efficacy without formal statistical hypothesis testing that aimed to show whether the efficacy profile of the two vamorolone doses is comparable to prednisone and deflazacort. The results were planned to be presented by summarizing the treatment differences and 95% confidence intervals (CIs) for all endpoints.

The efficacy endpoints were compared for each vamorolone dose versus the matched external controls from the FOR-DMD study and analysed using the mixed model for repeated measures (MMRM) model, observed data (i.e., without imputation as there was no control group at 48 weeks), and modified intent to treat analysis set 2 (mITT-2). The MMRM included the response values (as changes from baseline) from Weeks 24 and 48 as dependent values. The model included fixed effects for baseline age (as stratified in randomization), treatment group (vamorolone 2 mg/kg, vamorolone 6 mg/kg, prednisone 0.75 mg/kg), week (Week 24 or 48) and treatment-by-week interaction. The baseline value was included as a covariate. Within this model, pairwise comparisons (using least square mean [LSM] contrasts) were made to compare the treatment difference between vamorolone 6 mg/kg or 2 mg/kg with the FOR-DMD prednisone and deflazacort groups. An unstructured covariance structure was applied for MMRM. If this analysis failed to converge, Akaike's information criterion were used to select the best covariance structure

from compound symmetry and autoregressive-1 (AR [1]). The denominator degrees of freedom were computed using the Kenward-Roger method. The observations were weighted by the weights generated using propensity scores.

Subject matching for the safety comparison

All subjects who completed Treatment Period 1 and received at least one dose of vamorolone during Treatment Period 2 of VISION-DMD i.e., safety set 2 (SAF-2 set) were considered for matching. For the purpose of the safety comparisons, the subset of subjects meeting the common inclusion criteria of all studies was used. Therefore, the following criteria were used to select this matched patient population across the studies:

- Subjects with confirmed DMD.
- Age between 4 and < 7 years old at Baseline.
- Able to walk independently (based on inclusion criterion).
- Able to complete TTSTAND without assistance.

Safety Analyses

The safety comparison focused on endpoints that are common when assessing safety of glucocorticoid drugs. The evaluation was based on AE recordings. In addition, safety endpoints based on specific assessments were evaluated.

The TEAEs were tabulated by using the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT). Descriptive summaries of AE incidences (including point-and interval estimates of the treatment arm difference) are provided. The following were included in the AE summaries:

- The number of reported TEAEs (event count).
- The annualized rate of TEAEs, calculated as event count divided by the exposure to study medication (expressed as subject-years).
- The number and percentage of subjects reporting each TEAE at least once (subject count).

The incidence and frequency of all clinically relevant TEAEs meeting any of the following criteria was evaluated:

- Severity of Grade 2 and higher (moderate severity or higher)
- TEAE leading to premature discontinuation of study treatment.
- Serious TEAE

In addition, the AESI that represent known side effects of glucocorticoid drugs were identified using a broad search strategy of customized MedDRA queries. These were the same AESIs as had been prespecified for the VISION-DMD study and were detailed as predictable AEs in the FOR-DMD protocol.

Height was also prespecified as a safety endpoint of special interest and evaluated as follows:

- On the original scale
- As z-scores
- As percentiles.

The z-scores and percentiles were derived with methods similar to the original studies - the growth charts by Centres for Disease Control and Prevention (CDC) were used for derivation of z-scores and percentiles.

Each endpoint was summarized with descriptive statistics by visit. Visits common to all studies were used, including Baseline, Month 3 (week 12), Month 6 (Week 24), and Month 12 (Week 48).

In addition to the descriptive statistics, the data were evaluated using a restricted maximum likelihood based MMRM using the observed cases. The MMRM includes the response values (as changes from Baseline) from all applicable visits as dependent values. The model includes fixed effects for treatment group, month and the treatment-by-month interaction. The Baseline value was included as a covariate. Within this model, pairwise comparisons (using LSM contrasts) were made to compare the treatment differences at the different visits between vamorolone and daily prednisone and vamorolone and daily deflazacort. An unstructured covariance structure was applied for MMRM. If this analysis failed to converge, Akaike's information criterion was used to select the best covariance structure from compound symmetry and AR (1). The denominator degrees of freedom were computed using the Kenward-Roger method.

Investigation of the Validity of the External Comparisons

The subjects randomised to prednisone who met the common inclusion criteria were compared across studies in VISION-DMD Period 1 and the first 6 months of FOR-DMD to test the validity of the external control and provide additional context for interpretation of the FOR-DMD data.

For efficacy, all 31 subjects randomized to prednisone in VISION-DMD were matched to 37 subjects treated with prednisone in FOR-DMD. For safety, all 31 subjects randomized to prednisone in VISION DMD were matched to 50 subjects treated with prednisone in FOR-DMD.

7.1.3 Results from the comparative analysis

Data sets analysed

Of the 60 subjects randomised to vamorolone 2 or 6 mg/kg in Period 1 of VISION-DMD, 2 subjects in the vamorolone 6 mg/kg arm were excluded from the safety matched population as they never received treatment in the study (parental consent was withdrawn for 1 subject and 1 subject was found to meet an exclusion criterion, confounding previous or ongoing medical condition [had abnormality on Screening eye examination]). Additionally, 2 subjects in the vamorolone 2 mg/kg arm were excluded from the safety matched population as they did not receive any treatment in Period 2 (consent was withdrawn for both subjects).

Of the 130 subjects in the prednisone or deflazacort arms of the FOR-DMD study, 109 met the inclusion criteria for safety matching. Of these 109, 2 subjects in the

prednisone arm and 1 subject in the deflazacort arm were never treated and were therefore excluded from the safety matched population.

For safety, a total of 162 subjects were matched based on the main inclusion criteria (for safety analyses), and 139 subjects were also matched based on the propensity scores (for efficacy analyses) and comprised the populations for the external comparisons (Table 17).

Table 17 Analysis Sets for external comparison of VISION-DMD and matched subjects in FOR-DMD Study

	VISION-DMD	FOR-DMD	
	Vamorolone 6.0 mg/kg/day	Prednisone 0.75 mg/kg/day	Deflazacort 0.90 mg/kg/day
Randomised	[redacted]	[redacted]	[redacted]
Not matched for Safety comparison	[redacted]	[redacted]	[redacted]
Not treated	[redacted]	[redacted]	[redacted]
Not treated in VISION-DMD- Period 2	[redacted]	[redacted]	[redacted]
Age <4 or >7 years	[redacted]	[redacted]	[redacted]
Missing pretreatment TTSTAND without assistance or 6MWT	[redacted]	[redacted]	[redacted]
DMD not confirmed	[redacted]	[redacted]	[redacted]
Matched safety population for comparison	[redacted]	[redacted]	[redacted]
Matched for efficacy analyses on propensity score	[redacted]	[redacted]	[redacted]

Abbreviations: N/A = Not applicable; mg = milligram; kg = kilogram; TTSTAND = Time to stand test; 6MWT = 6-minute walk test. Source: [78]

Results

Table 18 Results from the comparative analysis of vamorolone vs prednisone and deflazacort for boys with DMD

Outcome measure	Vamorolone	Comparator	Result
TTSTAND (Month 6)	[redacted]	[redacted]	[redacted]
TTSTAND (Month 6)	[redacted]	[redacted]	[redacted]
TTSTAND (Month 12)	[redacted]	[redacted]	[redacted]

TTSTAND (Month 12)	[redacted]	[redacted]	[redacted]

aThe LSM change from baseline at Month 6 for the internal prednisone control was 0.07 rises/sec.
The observations are weighted by the weights generated using propensity scores. The LSM estimates are derived from a REML-based MMRM model with enrollment stratification age group (4-5 years; 6-<7 years), treatment (vamorolone 2.0 mg/kg/day, vamorolone 6.0 mg/kg/day, prednisone 0.75 mg/kg/day and deflazacort), week, baseline response, and the treatment-by-week interaction. Study week was included in the model as a categorical variable (Weeks 24 and 48 for VISION-DMD and Months 6 and 12 for FOR-DMD) along with the treatment-by-week interaction. An unstructured covariance structure was used, and the Kenward-Roger approximation was used to estimate denominator degrees of freedom.
Abbreviations: CI = Confidence Interval; LMS = Least Square Mean; SD = Standard Deviation; SE = Standard error; TTSTAND = Time to Stand Test; mg = milligram; kg = kilogram; N = Number of subjects. Source: [78]

7.1.4 Efficacy – results per TTSTAND

The results for TTSTAND velocity are shown in Table 18 and Figure 7 and summarised in this section. TTSTAND velocity had increased in the vamorolone 6.0 mg/kg/day, prednisone, and deflazacort groups at Months 6 and 12. [redacted] [83].

There were no significant differences between vamorolone 6.0 mg/kg/day and either prednisone or deflazacort in TTSTAND velocity at Month 6 or Month 12 (Table 18, Figure 7). The minimal clinically important difference (MCID) in TTSTAND velocity has been reported as 0.023 rises/sec [84]. [redacted] [83]. Therefore, the results indicate that vamorolone 6.0 mg/kg/day, prednisone and deflazacort have comparable efficacy in TTSTAND velocity.

Figure 7 Mean (SEM) change in TTSTAND velocity from baseline in vamorolone compared with prednisone and deflazacort

[redacted]

Abbreviations: TTSTAND = Time to stand test; DFZ = deflazacort; PDN = prednisolone: SEM = standard error of mean; VAM = vamorolone; mg = milligram; kg = kilogram. Source: [85]

7.1.5 Efficacy – results per other motor function endpoints.

TTSTAND velocity, as explained before, was the key efficacy endpoint for the comparison. Other compared motor function endpoints included TTRW velocity, 6MWT and NSAA. These measures demonstrated comparable benefits with vamorolone 6mg/kg/day as with prednisone and deflazacort at 6 and 12 months. Vamorolone did not show statistically different results to prednisone or deflazacort, with the exception of NSAA score for vamorolone vs deflazacort at month 12. However, the difference was below the MCID. The detailed results of these comparisons are found in **Error! Reference source not found.**.

8. Modelling of efficacy in the health economic analysis

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

8.1.1 Extrapolation of efficacy data

This section is not applicable because there has been no extrapolation of efficacy data. It is assumed that vamorolone and traditional glucocorticoid therapy (prednisolone and deflazacort) have comparable efficacy, based on the results from VISION-DMD in section 6.1.4 and the results from the matched comparison in section 7.1.3.

8.1.1.1 Extrapolation of [effect measure 1]

Table 19 Summary of assumptions associated with extrapolation of [effect measure]

Method/approach	Description/assumption
Data input	N/A

8.1.1.2 Extrapolation of [effect measure 2]

This section is not applicable.

8.1.2 Calculation of transition probabilities

This section is not applicable because transition probabilities were not calculated from the clinical data (VISION-DMD and FOR-DMD) presented in section 6 and section 7.

Table 20 Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference

N/A	N/A	N/A	N/A

8.2 Presentation of efficacy data from Natural History Model

The same transition probabilities have been assumed for vamorolone, prednisolone and deflazacort, since comparable efficacy has been demonstrated between them (section 6.1.4 and section 7.1.3). The calculation of transition probabilities is described below.

8.2.1 Calculation of transition probabilities

The transition probabilities are based on a Natural History Model (NHM) developed by Project HERCULES (a project to develop tools and evidence to support HTA for DMD treatment) [58]. The primary data source used was the Critical Path Institute (C-Path) Duchenne Regulatory Science Consortium (D-RSC) database [86]. The C-Path D-RSC comprises patient-level multinational clinical data for DMD and is comprised of individual patient-level data (IPD) from 11 international data sources, DNHS, placebo arms of clinical trials, and registry data. The patient cohort used to generate the NHM comprised of 80% of patients on corticosteroids. The treatment name and dosing scheme were not stated, which is a limitation of the NHM.

The NHM assumed that DMD is progressive, with a constant progression rate in each state, no backwards transitions permitted, and that patients may only progress to adjacent states [59]. The assumptions were validated through UK-based clinician interviews [87].

The health stages in the model have been previously described in section 4.1. There were very few transitions observed into or out of state 3 ('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 [59]. This could be because in order to be assigned to states 3 or 4, a NSAA score (of 1 or 0, respectively) must be recorded, but if the patients are classed by clinicians as non-ambulatory, then the NSAA is unlikely to have been conducted [59].

Due to the paucity of data pertaining to health states 3, 4, 5 and 6 in the dataset, an elicitation approach was used to inform transition intensities [59]. This included an initial pilot, in which information was elicited from four clinicians and four caregivers. This was followed by an online survey of Duchenne UK stakeholders, with 20 responses from DMD parents, caregivers and practitioners. Using a questionnaire, respondents were asked to describe the average age at which patients enter and exit health states. From the responses received, the mean age and standard deviation for entering and exiting the states was estimated [59]. These data were then used to simulate IPD from which transition intensities could be estimated [88]. Where some transitions were observed in the D-RSC dataset, the simulated IPD were used to augment rather than replace these data [59].

The transition intensities were estimated via the following six steps [59]:

(1) The mean age of patients observed in each state in the D-RSC dataset was estimated.
(2) To estimate the mortality rate for each state, a piecewise constant hazard function was fitted to the mortality data, with cut points determined by the mean age in each state.
(3) 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.
(4) A multistate model was fitted in R using the msm package using the specified transition intensity matrix and fixing mortality rates at their initial values.
(5) A new transition intensity matrix was then defined using the transition intensities estimated in Step 4 and mortality rates estimated in Step 2.
(6) Steps 4 and 5 were then 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. The use of the piecewise exponential facilitated implementation of an increased rate of mortality after age 30 years in the full-time ventilation states. Age 30 years was selected as a mid-point in the follow up, approximately corresponding to the median survival of patients in the mortality dataset and in the published literature [89, 90]. Table 21 and Table 22 present the transition intensities produced by the NHM, split by patients under and over the age of 30, respectively.

Table 21. Transitions in the health economic model (patients below 30 years)

	State 1	State 2	State 3	State 4	State 5	State 7A	State 8A	State 6	State 7B	State 8B	State 9	Description of method and Reference
State 1	98.64%	1.36%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	Transition probabilities are based on IPD from the The C-Path D-RSC database. State 3,4, 5 and 6 are informed by data from an elicitation exercise. The NHM fit was iterated until convergence was achieved for all
State 2	0.00%	97.61%	2.38%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.01%	
State 3	0.00%	0.00%	94.72%	5.27%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.01%	
State 4	0.00%	0.00%	0.00%	95.30%	2.37%	0.00%	0.00%	2.28%	0.00%	0.00%	0.05%	
State 5	0.00%	0.00%	0.00%	0.00%	98.25%	1.64%	0.00%	0.00%	0.00%	0.00%	0.11%	
State 7a	0.00%	0.00%	0.00%	0.00%	0.00%	96.45%	3.29%	0.00%	0.00%	0.00%	0.25%	
State 8a	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	99.67%	0.00%	0.00%	0.00%	0.33%	
State 6	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	98.24%	1.51%	0.00%	0.24%	
State 7b	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	95.59%	4.11%	0.30%	

State 8b	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	99.68%	0.32%	transition rates. [59]
State 9	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	100.00%	

Table 22. Transitions in the health economic model (patients above 30 years)

	State 1	State 2	State 3	State 4	State 5	State 7A	State 8A	State 6	State 7B	State 8B	State 9	Description of method and Reference
State 1	98.64%	1.36%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	Transition probabilities are based on IPD from the The C-Path D-RSC database. State 3,4, 5 and 6 are informed by data from an elicitation exercise. The NHM fit was iterated until convergence was achieved for all transition rates. [59]
State 2	0.00%	97.61%	2.38%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.01%	
State 3	0.00%	0.00%	94.72%	5.27%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.01%	
State 4	0.00%	0.00%	0.00%	95.30%	2.37%	0.00%	0.00%	2.28%	0.00%	0.00%	0.05%	
State 5	0.00%	0.00%	0.00%	0.00%	98.25%	1.64%	0.00%	0.00%	0.00%	0.00%	0.11%	
State 7a	0.00%	0.00%	0.00%	0.00%	0.00%	96.45%	3.29%	0.00%	0.00%	0.00%	0.25%	
State 8a	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	99.35%	0.00%	0.00%	0.00%	0.65%	
State 6	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	98.24%	1.51%	0.00%	0.24%	
State 7b	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	95.59%	4.11%	0.30%	
State 8b	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	99.35%	0.65%	
State 9	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	100.00%	

8.3 Modelling effects of subsequent treatments

This section is not applicable – no subsequent treatments are included in the model.

8.4 Other assumptions regarding efficacy in the model

This section discusses the impact of down-titration in the health economic model.

Prednisolone and deflazacort down-titration

Down-titration for prednisone and deflazacort was estimated from the Cooperative International Neuromuscular Research Group (CINRG) data set, based on a Kaplan-Meier (KM) analysis assessing the proportion of patients still on initial treatment dosage over a period of 14 years (**Error! Reference source not found.**) [91]. As both KM curves are complete, there was no need to extrapolate the data further [91]. Data on the average dose received for each treatment arm were also taken from the CINRG data set to ensure consistency in sources (**Error! Reference source not found.**) and used to calculate the dose received per cycle. Prednisone patients started on a dose of 0.75 mg/kg/day and those on deflazacort started on 0.9 mg/kg/day.

Figure 8 [redacted]

[redacted]

Figure 9 [redacted]

[redacted]

Vamorolone down-titration

The base case model assumes [redacted] of vamorolone patients down-titrate from 6 mg/kg to 4 mg/kg. This is based on evidence from VISION-DMD where the occurrence of treatment emergent adverse events (TEAEs) during the 12-month period was low (see section 9.1.2 for further detail).

Impact of down-titration in the model

The base case in the model assumes [redacted] The model assumes a [redacted] loss of efficacy for patients receiving glucocorticoids. This was derived by calculating the difference in starting dose and average dose (the latter by age, up until the median age of death from the Natural History Model, using CINRG data) received by prednisolone and deflazacort patients, respectively, and then taking the average of these differences to reach [redacted] [91]. [redacted]. This approach is based on clinical validation by UK experts [87] and aligns with what has been found in clinical studies [5, 43].

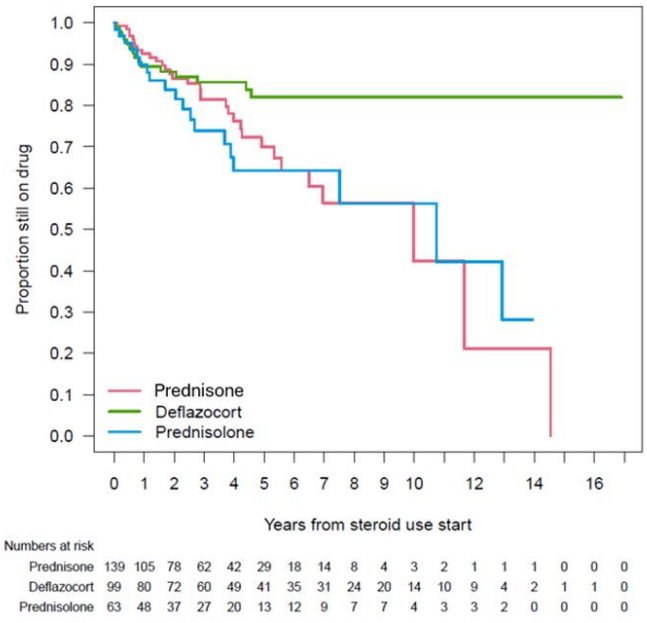
8.5 Overview of modelled average treatment length and time in model health state

To manage side effects of corticosteroids, patients may discontinue treatment entirely. Discontinuation data for prednisolone and deflazacort were taken from the CINRG data set based on a KM analysis, shown in Please note, this discontinuation extrapolation is to account for patients who discontinue treatment due to side effects. The model also has the option to apply a stopping rule for vamorolone, prednisolone and deflazacort patients, where patients are treated until a specific disease milestone. In the base case, all patients are treated until death (see section 11.1 for more detail).

Figure 10. As the KM data are not complete, discontinuation in the model is exponentially calculated using the GROWTH function in Excel. Discontinuation for vamorolone patients is based on VISION DMD data and similarly extrapolated exponentially using the GROWTH function.

Please note, this discontinuation extrapolation is to account for patients who discontinue treatment due to side effects. The model also has the option to apply a stopping rule for vamorolone, prednisolone and deflazacort patients, where patients are treated until a specific disease milestone. In the base case, all patients are treated until death (see section 11.1 for more detail).

Figure 10 Prednisone and deflazacort discontinuation KM from CINRG



Abbreviations: CINRG = Cooperative International Neuromuscular Research Group; KM = Kaplan-Meier

Given the model structure, Table 23 is not applicable and Table 24 only includes information on treatment length. Note that scenario analyses for different treatment lengths are presented in Appendix L.

Table 23 Estimates in the model

	Modelled average [effect measure] (reference in Excel)	Modelled median [effect measure] (reference in Excel)	Observed median from relevant study
[Name of intervention]		N/A	

Table 24 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction (adjust the table according to the model)

Treatment	Treatment length (years, mean)	Health state 1 [months]	Health state 2 [months]
Vamorolone	xxx		N/A
Prednisolone	xxxx		N/A
Deflazacort	xxxxxx		N/A

Note: that a scenario analysis with different treatment durations is included in Appendix L..

9. Safety

9.1 Safety data from the clinical documentation

9.1.1 Safety outcomes from VISION-DMD

Treatment-emergent adverse events

In VISION-DMD, period 1 (24 weeks) was prednisone-controlled, and therefore the overview of AEs in Table 25 is presented for period 1. The analysis population for safety at Week 24 was the Safety-1 population, which included 118 subjects who received at least one dose of study medication during Period 1. The duration of exposure and total exposure during Period 1 (24 weeks) were similar for the vamorolone group compared with the placebo and prednisone groups.

In the study, TEAEs are defined as any AE starting or worsening after initiation of the investigational product and through the subject's last study visit (study completion or early termination). AEs exclusively connected to the study drug are defined as "drug-related TEAEs".

The analysis population for safety at Week 48 was the Safety-2 population, which included 114 subjects who completed Period 1 and received at least one dose of vamorolone during Period 2. Overview of safety events for the Safety-2 population is presented in Table 26, and an overview of TEAEs in the vamorolone group during Period 1 is compared with Period 2 in Table 96 (Appendix K). Vamorolone was well tolerated during 48 weeks of treatment. The majority of TEAEs were mild or moderate, and there was no reported death.

Table 25 Overview of safety events VISION-DMD (Study period 1 – 24 weeks)

	Vamorolone 6.0mg/kg/day (N=28)	Placebo (N=29)	Prednisone 0.75mg/kg/day (N=31)	Difference, % (95 % CI)
Number of adverse events, f(Rate)	[redacted]	[redacted]	[redacted]	[redacted]
Patients with ≥1 adverse events, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Number of serious adverse events*, n	[redacted]	[redacted]	[redacted]	[redacted]
Patients with ≥ 1 serious adverse event*, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Number of CTCAE grade ≥ 3 events, f(Rate)	[redacted]	[redacted]	[redacted]	[redacted]
Patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Number of drug-related TEAEs, f(Rate)	[redacted]	[redacted]	[redacted]	[redacted]
Patients with ≥ 1 drug-related TEAEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Patients who had a dose interruption, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Patients who had a dose reduction, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Patients who discontinue treatment regardless of reason, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Patients who discontinue treatment due to adverse events, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect.
§ CTCAE v. 5.0 must be used if available. Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; TEAE = Treatment-emergent adverse event; N/A = Not applicable; CI = Confidence interval; N = number of subjects. Source: [74]

Table 26 Overview of safety events VISION-DMD (Study period 2 – 48 weeks)

	Vamorolone 6.0mg/kg/day (N=28)	Placebo+ vamorolone 6.0mg/kg/day (N=14)	Prednisone 0.75mg/kg/day+ vamorolone 6.0mg/kg/day (N=15)	Difference, % (95 % CI)
Number of adverse events, f (Rate)	Xxxxxxx	xxxxXx	Xxxxxx	Xxx
Patients with ≥1 adverse events, n (%)	Xxxxxxxx	Xxxxxx	Xxxxxxxx	Xxx
Number of serious adverse events*, n	Xxxxx	Xxxx	Xxxxx	Xxxx
Patients with ≥ 1 serious adverse event*, n (%)	Xxxx	Xxxxx	Xxx	Xxx
Number of CTCAE grade ≥ 3 events, f(Rate)	Xxx	Xxx	xxXx	Xxx
Patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	xxxX	Xxxxx	Xxxxx	Xxxx
Number of drug-related TEAEs, f(Rate)	Xxxxxx	Xxxxx	Xxxx	xxx
Patients with ≥ 1 drug-related TEAEs, n (%)	Xxxx	Xxxxx	Xxxx	Xxx
Patients who had a dose interruption, n (%)	Xxxxxxxx	Xxx	Xxxxxxxx	xxxx
Patients who had a dose reduction, n (%)	Xxxxx	Xxxx	Xxxxx	Xxxx
Patients who discontinue treatment regardless of reason, n (%)	Xxxx	Xxxxx	Xxx	Xxx
Patients who discontinue treatment due to adverse events, n (%)	Xxx	Xxx	Xxxxxx	Xxx

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect.
§ CTCAE v. 5.0 must be used if available. Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; TEAE = Treatment-emergent adverse event; N/A = Not applicable; CI = Confidence interval; N = number of subjects. Source: [74]

Height at Week 24

Growth stunting was not seen with vamorolone but was seen with prednisone. Mean height was below average at baseline, as expected for children with DMD. Height, height percentile, and height z-score increased in the vamorolone and placebo groups in Period 1 (Table 97, Appendix K). The LSM differences for height, height percentile and height z-score for the vamorolone 6.0 mg/kg/day group and the placebo group at Week 24 were

not statistically significant (Table 27). Decreases in height, height percentile, and height z- were seen in the prednisone group score (Table 97, Appendix K). [redacted]

Table 27 MMRM analysis of change from baseline in height at Week 24 (Period 1, SAF-1)

Comparison	n	LSM (SE)	LSM Difference (SE)	LSM Difference 95% CI	p-value
Height (cm)					
Vamorolone 6.0 mg/kg/day vs. Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone 6.0 mg/kg/day vs. Prednisone 0.75mg/kg/day	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Height percentile					
Vamorolone 6.0 mg/kg/day vs. Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone 6.0 mg/kg/day vs. Prednisone 0.75mg/kg/day	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Height z-score					
Vamorolone 6.0 mg/kg/day vs. Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vamorolone 6.0 mg/kg/day vs. Prednisone 0.75mg/kg/day	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

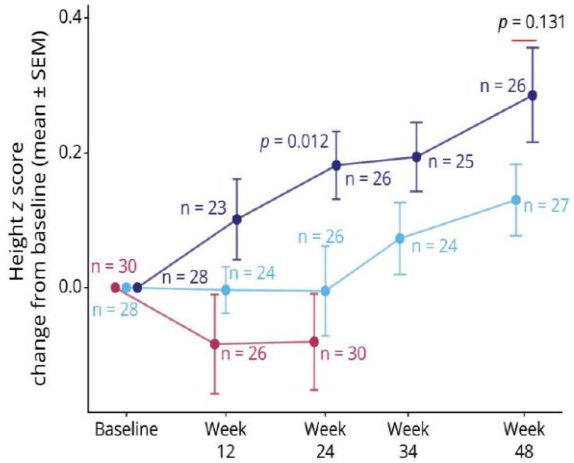
Note: Baseline is defined as the last measurement taken prior to first exposure to study drug, including Day 1 measurements taken pre-dosing. The LSM estimates are derived from a restricted maximum likelihood (REML)-based MMRM model with treatment, enrolment stratification age group (4-5 years, 6-<7 years), week, baseline response, and the treatment-by-week interaction. Study week is included in the model as a categorical variable along with the treatment-by-week interaction. An unstructured covariance structure is used. The Kenward-Roger approximation is used to estimate denominator degrees of freedom. Abbreviations: MMRM = mixed model for repeated measures; n = number of subjects with a valid response; LSM = least squares mean; SE = standard error; CI = confidence interval; cm = centimetre. Source: [74]

Height at Week 48

Patients treated with vamorolone for 48 weeks showed normal growth trajectories. The change in height z-score continued to increase in the vamorolone 6.0 mg/kg/day group

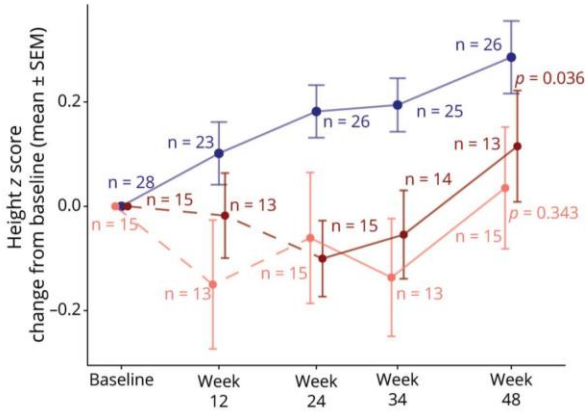
(0.18 SD in Period 1 to 0.29 SD in Period 2). No stunting of growth was observed with either vamorolone doses. Mean (SD) change from baseline to week 48 for vamorolone 2.0mg/kg/day and 6.0 mg/kg/day was 0.13 (0.277) and 0.29 (0.355) respectively, in contrast to stunting of growth known to occur with corticosteroids [92]. Growth stunting with the recommended dose of prednisone treatment over 24 weeks is shown in Figure 11. During the cross over of prednisone-treated patients to vamorolone, the stunting of growth seen with prednisone in Period 1 was reversed following the switch to either vamorolone 2.0 or 6.0 mg/kg/day in Period 2 and experienced catch-up growth (Figure 12). The change from baseline in height z-score increased from -0.06 SD during prednisone treatment to +0.04 SD (+0.1 SD at 24 weeks) at 48 weeks in the vamorolone 2.0 mg/kg/day group and from -0.10 SD to +0.12 SD (+0.22 SD at 24 weeks) in the vamorolone 6.0 mg/kg/day group meaning that these subjects grew faster than the CDC reference population and moved up to higher percentile lines in the growth.

Figure 11 Change in height z-score with prednisone over 24 weeks and vamorolone over 48 Weeks



Note: dark blue = vamorolone 6.0 mg/kg/day, light blue = vamorolone 2.0 mg/kg/day; red = prednisone 0.75 mg/kg/day. Unadjusted mean values and SEs are plotted using the safety- 2 population. P values are provided for LSM comparisons from MMRM between the vamorolone dose groups over 48 weeks of treatment (safety-2 population). For context, a p value is overlaid for 24 weeks of treatment for comparison of LSM for prednisone (period 1) and vamorolone 6.0 mg/kg/day using the safety-2 population. Abbreviations: SEM = Standard error of mean; LSM = least squares mean; 2; MMRM = mixed model for repeated measures. Source: [18]

Figure 12 Change in height z-score following the switch from prednisone 0.75 mg/kg/day to vamorolone over 48 weeks



Note: orange = prednisone 0.75 mg/kg/day -> vamorolone 2.0 mg/kg/day; red = prednisone -> vamorolone 6.0 mg/kg/day; blue = vamorolone 6.0 mg/kg/day. P values are provided for within-group change for the prednisone crossover groups from week 24 (start of washout) to week 48 (including 20 weeks of treatment). Note that 1 time point (week 12 each time) for 3 participants (1 from vamorolone 2.0 mg/kg/day and 2 from vamorolone 6.0 mg/kg/day group) were removed because of suspected recording errors: patients had changed height by >10 cm by week 12 assessment, and future time points showed regression back closer to baseline height. Analysis including these values provided very similar findings and do not change interpretation. Color-coded (corresponding to legend) sample sizes at each time point are overlaid. Abbreviations: SEM = Standard error of mean; LSM = least squares mean; 2; MMRM = mixed model for repeated measures. Source: [18]

Bone biomarkers at Week 24

Bone biomarkers indicated an improved safety profile of vamorolone on bone health compared with prednisone at Week 24. Biomarkers for osteoblast activity ((osteocalcin and procollagen I N terminal propeptide (P1NP)) and osteoclastic activity (C-terminal telopeptide of type 1 collagen (CTX)) were measured to assess bone turnover. Mean and median changes from baseline to Week 24 for osteocalcin, P1NP, and CTX were small and similar in the vamorolone 6 mg/kg groups compared with the placebo group (Table 98: Appendix K) none of the LSM differences for the vamorolone groups from the placebo group were statistically significant (Table 99, Appendix K). In contrast, significant reductions from baseline to Week 24 were seen in all bone biomarkers for the prednisone group compared with each vamorolone group (Table 28).

Table 28 Change from baseline in bone biomarkers at week 24 in the prednisone group compared with the vamorolone group (Safety-1 Population)

	Prednisone 0.75mg/kg/day (N=31)	Vamorolone 6.0 mg/kg/day (N=28)
Osteocalcin		
n	23	22
Mean change from baseline	-15.50	-0.17
LSM (SE) change from baseline	-15.5207 (2.7979)	1.5972 (2.8934)
LSM difference (SE)		17.1179 (3.9307)
95% CI		9.2979, 24.9379
p value		<0.0001
P1NP		
n	23	23
Mean change from baseline	-143.73	-7.93
LSM (SE) change from baseline	147.143 (22.3526)	-18.3371 (22.3855)
LSM difference (SE)		128.8061 (31.0068)
95% CI		67.1214, 190.4907
p value		<0.0001
CTX		
n	24	23
Mean change from baseline	-320.3	110.2
LSM (SE) change from baseline	-313.300	80.4502

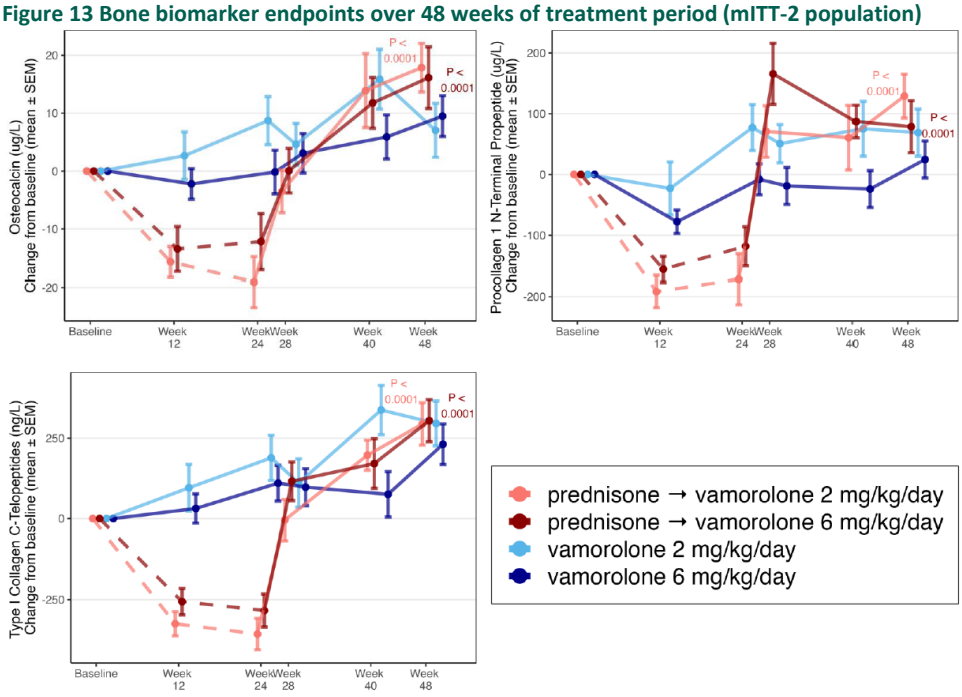
	(44.1723)	(45.1124)
LSM difference (SE)		393.7500 (61.4232)
95% CI		271.6281, 515.8719
p value		<0.0001

Abbreviations: CI = Confidence interval; LSM = Least square mean; P1NP = Procollagen type 1 N-terminal propeptide; SE = Standard error; CTX- = C-terminal telopeptide of type 1 collagen; CI = Confidence interval; SE = Standard error; N = Number of subjects; mg = milligram; kg = kilogram.

Bone biomarkers at 48 weeks

With vamorolone 6.0 mg/kg/day treatment for 48 weeks, the serum concentration of osteocalcin increased slightly from Week 24 to Week 48, P1NP remained at baseline levels, and CTX continued to increase mildly (Table 100, Appendix K). During the cross over of prednisone-treated patients to vamorolone, serum osteocalcin, P1NP, and CTX, that were all depressed by prednisone treatment during Period 1, recovered swiftly after switching to vamorolone 2.0 mg/kg/day or vamorolone 6.0 mg/kg/day (
Figure 13) (Table 100, Appendix K).

Figure 13 Bone biomarker endpoints over 48 weeks of treatment period (mITT-2 population)



Note: Unadjusted means and SEs are plotted using the mITT-2 population. On the figures, p-values are provided for within-group change for the prednisone crossover groups from Week 24 (start of washout) to Week 48 (including 20 weeks of treatment). Abbreviations: SAF-2 = Safety period 2 population; SEM = Standard error of mean; mg = milligram; kg = kilogram; mITT = modified Intention to treat. Source: [18]

Behavioural changes

Behavioural problems were reported in a lower percentage of subjects in the vamorolone groups compared with the prednisone group (Table 29). This difference between the groups was not due to a single AE, but a number of different AEs that were reported in 1 subject each, including a number of AEs related to more aggressive behaviour. The severity of the behaviour problems in the prednisone group was higher than in the vamorolone

and placebo groups. One subject from the prednisone group discontinued the study because of personality change. One subject from the prednisone group discontinued the study because of aggression. There was no moderate or severe behaviour problem TEAE in the vamorolone 6.0 mg/kg/day group over 12 months and no behaviour problem led to discontinuation. During the cross over of prednisone-treated patients to vamorolone to vamorolone 6.0 mg/kg/day, a decrease in behavioural problems was observed Table 29.

Table 29 Behaviour problems in Period 1 (Safety-1 Population)

Behaviour problems	Placebo (N=29) n (%)	Prednisone (N=31) n (%)	Vamorolone 6.0 mg/kg (N=28) n (%)
Behaviour problems	4 (13.8)	10 (32.3)	6 (21.4)
Irritability	0	1 (3.2)	3 (10.7)
Abnormal behaviour	1 (3.4)	2 (6.5)	1 (3.6)
Aggression	1 (3.4)	2 (6.5)	1 (3.6)
Agitation	0	0	1 (3.6)
Anxiety	0	0	1 (3.6)
Mood altered	0	0	1 (3.6)
Sleep disorder	1 (3.4)	1 (3.2)	1 (3.6)
Anger	0	1 (3.2)	0
Emotional disorder	0	1 (3.2)	0
Mood swings	1 (3.4)	1 (3.2)	0
Poor quality sleep	0	0	0
Psychomotor hyperactivity	0	3 (9.7)	0
Skin laceration[1]	0	0	0

Note: Treatment-emergent adverse events (TEAEs) are defined as any adverse event starting or worsening after initiation of the investigational product and through the subject's last study visit (study completion or early termination). For the Period #1 analyses, AEs, SAEs and TEAEs with onset through the subject's Week 24 F/U Visit are included. Table is sorted in descending order of PTs in the vamorolone 6.0 mg/kg/day group.
1 Occurred with a fall and was not a behaviour problem. Abbreviations: n = Number of subjects; mg = milligram; kg = kilogram.

Table 30 Behavioural problems following the switch from placebo or prednisone in Period 1 to vamorolone in Period 2 (Safety-2 Population)

Behaviour problems	Prednisone 0.75mg/kg/day Period 1 (N=15)	Vamorolone 6.0 mg/kg/day Period 2 (N=15)
Behaviour problems	6 (40.0)	3 (20.0)

Abbreviations: N = Number of subjects; mg = milligram; kg = kilogram.

9.1.2 Safety outcomes from the matched comparison of VISION-DMD and FOR-DMD

TEAE

The majority of subjects experienced TEAEs during the 12-month period in the VISION-DMD and FOR-DMD studies. The results are summarised below:

- [redacted]The overall incidence of TEAEs was generally [redacted] for vamorolone 6.0 mg/kg/day in the VISION-DMD study and prednisone or deflazacort in the FOR-DMD study (Table 101, Appendix K)
- Serious TEAEs were infrequent [redacted] in the prednisone and vamorolone groups) but occurred more frequently in the deflazacort group (Table 101, Appendix K).
- The frequency of TEAEs leading to study drug discontinuation was low and comparable between the groups (Table 101, Appendix K). Expected events leading to discontinuation of treatment with glucocorticoids, i.e., Cushingoid, weight increase and behaviour problems, were reported in prednisone and deflazacort groups but not in the vamorolone groups after 12 months (Table 102, Appendix K).
- Severe TEAEs were more frequently reported in the prednisone and deflazacort than in vamorolone groups over 12 months (Table 103, Appendix K).
- Ocular hypertension was reported in 1 subject in the deflazacort group. Otherwise no subject presented with cataracts or glaucoma during the first 12 months treatment.
- Consistent with the results by SOC, vamorolone presented a [redacted]
- The pattern of behaviour disorders was different in the vamorolone 6 mg/kg group compared to the prednisone or deflazacort groups: [redacted]
- The incidence of TEAEs [redacted] across the treatment groups for most of the SOCs (Table 104, Appendix K). [redacted] [83].

Height

The results for height are summarised in Figure 14 and elaborated in Table 105, Appendix K). At Month 6, consistent with the results of the VISION-DMD study, subjects in the vamorolone 2.0 or 6.0 mg/kg/day groups had a positive height increase in percentile and z-score change, while negative values were observed in the prednisone group. The baseline values and changes in height z-scores were comparable in the prednisone groups in the VISION-DMD study and the FOR-DMD study indicating valid external comparisons can be made. After 12 months, the height z-scores in the vamorolone 2.0 mg/kg/day group had increased by 0.18 SD and in the 6.0 mg/kg/day group by 0.29 SD suggesting growth similar or slightly higher than the pediatric reference population, whereas height z-score had decreased by [redacted] in the prednisone group and by [redacted] in the deflazacort group indicating growth stunting. These 12-month data confirm that vamorolone does not have a negative impact on height that is seen with prednisone and deflazacort.

Figure 14 [redacted]

[redacted]

Note: In the VISION-DMD study the population is patients who received 2.0/6.0 mg/kg/day from start of Period 1 and who continued to period 2. Model included visits as fixed months (Month 3, 6 and 12). In the figure the time is presented as weeks: FOR-DMD had visits at Months 3, 6 and 12, but VISION-DMD had at Weeks 12, 24 and 48; Abbreviations: LSM = least squared mean; MMRM = Mixed Model for Repeated Measures, SE = standard error; mg = milligram; kg = kilogram.

Safety data in the health economic model

Adverse events of special interest

The base case in the model is based on moderate/severe AESI. AESI of all grades are included in a scenario analysis. Moderate/severe and mild AE rates were sourced from the cumulative incidence of AEs in the 24-week VISION-DMD data for vamorolone and prednisone. AEs for deflazacort were assumed to be the same as prednisolone in the model, in the absence of data based on a head-to-head trial. The VISION-DMD rates used in the model are presented for moderate/severe and mild AESI, as seen in Table 31. Data were converted into a per cycle probability for use in the model. An associated QALY decrement were applied per each AE incidence (Table 40).

Acute events

The model captures short-term acute events sourced from VISION-DMD over 24 weeks for vamorolone 6.0 mg/kg/day and prednisone 0.75 mg/kg/day and. Given the lack of more relevant data, the acute events observed for prednisone 0.75 mg/kg/day in VISION-DMD were applied to deflazacort 0.9 mg/kg/day. The rates used in the model are presented below in Table 31. The data were converted into a per cycle probability for use in the model.

Table 31 Adverse events used in the health economic model

Adverse events	Intervention	Comparator	Comparator		
	Frequency used in economic model for vamorolone 6 mg/kg/day	Frequency used in economic model for prednisolone 0.75 mg/kg/day	Frequency used in economic model for deflazacort 0.9 mg/kg/day	Source	Justification
[redacted]					
[redacted]					
[redacted]					

Xxxxx					
Xxxxxx					
Xxxxxxx					
Xxxxx					
xxxxx					
Xxxxxxxxxxxxx					
Xxxxxx				Xx	Xxxxxx
Xxxxxx					
Xxxxxxx					
Xxxxxx					
Xxxxxx					
Xxxxx					
Xxxxx					
Xxxx					
				xxxx	xxxxx
Xxxxxxxxxxxxx					
	Xxxxx	Xxxx	Xxxx	Xxxxx	xxxx
	Xxxxx	Xxxxx	Xxxx		
	Xxxxx	Xxxxxx	Xxxxx		
	Xxx	Xxx	xxxx		

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

AE rates for scoliosis, fractures and stunted growth and from the literature and clinical input. This is elaborated on below.

Scoliosis

The model captured the impact of scoliosis via the proportion of patients requiring spinal fusion surgery, with a disutility associated with the surgery. Patients were eligible for spinal surgery in the model from 4 years following loss of ambulation based on McDonald et al., 2018, in which both chronic and non-chronic corticosteroid users had spinal surgery on average 4-5 years after loss of ambulation [6]. The study assessed the impact of long-term corticosteroid use on the quality of life of patients with DMD, and found that 72 of 248 (29%) non-ambulatory patients had spinal fusion surgery over 10 years. The study was largely comprised of patients who had been treated with glucocorticoids (only 13% had never been treated with glucocorticoids). However, UK clinical validation indicated that in clinical practice, nearer 10% of patients on corticosteroid treatment have spinal fusion surgery, whereas for patients who are off treatment, the rate is nearer 90%. Rates of spinal surgery provided by clinical experts were used in the model base case and are shown in Table 32. The risk of spinal surgery is assumed to remain constant across treatment arms, with patients not switching to a different rate when they discontinue or lower their dosing. Once a patient discontinues treatment, they move to the per cycle probability of spinal surgery associated with no treatment.

Fractures

Fracture rates for deflazacort and prednisolone patients in the model are based on FOR-DMD data. Symptomatic fractures for chronic corticosteroid use from Perera et al., 2016 [93] are used in combination with fracture rates for deflazacort and prednisone in FOR-DMD to calculate fracture rates for vamorolone. The probabilities for the chronic corticosteroid use were converted into incidences by age, which were then categorised into rates for health states based on the average ages for health states for the corticosteroid. The rates occur during the health states so the duration they are applicable to is the duration of the health state.

Stunted growth

Data on stunted growth were not available from either VISION-DMD or FOR-DMD. Rates of stunted growth for prednisolone and deflazacort were therefore based on Wong et al. 2016 [94]. Wong et al., 2016, a retrospective study from The Comprehensive Neuromuscular Centre at Cincinnati Children's Hospital Medical Centre, reported that 72% of boys with DMD experienced short stature over 6 years when taking glucocorticoids (inclusive of 89% daily deflazacort and 11% daily prednisone) [94]. This 72% rate in Wong et al., 2020 [94] was applied for prednisolone and deflazacort patients. This rate was then converted to a per cycle monthly probability [45].

Table 32. Adverse events used in the health economic model (source – literature/clinical input)

Adverse events	Intervention	Comparator			
	Frequency used in economic model for vamorolone	Frequency used in economic model for prednisolone	Frequency used in economic model for deflazacort	Source	Justification
Scoliosis					
% patients that receive spinal fusion surgery	10%	10%	10%	Based on clinical expert opinion.	In lieu of other data, vamorolone has been assumed to have the same rate as standard of care.
Time to surgery after loss of ambulation (years)	4	4	4	McDonald et al., 2018 [6]	Most had surgery on average 4 years in [6]
Fractures					
% patients with spinal vertebral fractures	21%	42%	78%	FOR-DMD and Perera et al., 2016 [93] [93]	Rates for deflazacort and prednisolone are based on FOR-DMD, while vamorolone is based on [93] and FOR-DMD.
Stunted growth					
Incidence per cycle	0%	1.75%	1.75%	Wong et al., 2020 [94]	This stunted growth rate in [94] was applied to deflazacort and prednisolone patients. The rate was then converted to a per cycle monthly probability [45].

Table 33 Adverse events that appear in patients

Adverse events	Intervention			Comparator			Difference, % (95 % CI)	
	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for intervention	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for comparator	Number of patients with adverse events	Number of adverse events
Adverse event, n								
Scoliosis	N/A	N/A	10% patients, assumption.	N/A	N/A	Prednisolone and deflazacort: 10% patients, assumption.	N/A	N/A
Fractures (spinal vertebral)	N/A	N/A	0%-0.64% per cycle, depending on health state [78, 93]	N/A	N/A	Prednisolone and deflazacort: 0%-1.36% per cycle, depending on health state [78]	N/A	N/A
Fractures (other)	N/A	N/A	0%-0.38% per cycle, depending on health state [78, 93]	N/A	N/A	Prednisolone and deflazacort: 0%-0.79% per cycle, depending on health state [78]	N/A	N/A
Stunted growth	N/A	N/A	0% patients	N/A	N/A	Prednisolone and deflazacort: 1.75% per cycle [94, 95]	N/A	N/A

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

The use of patient-reported outcome measures (PROMs) to determine HRQL is challenging in DMD [96, 97]. The HRQoL in DMD is substantially impaired compared to the general population and children with other chronic illnesses, particularly in physical domains. Despite severe physical impairments, many patients report relatively high levels of psychosocial well-being [98], [99]. Therefore, the effectiveness of PROMs in assessing HRQoL has been questioned. [100], [101]. A recent systematic review examining the content and structural validity of QoL tools used in DMD underscored that none of these measures have strong supporting evidence to establish their reliability and validity [97] .

PROMs for DMD cannot capture the multi-dimensionality of the disease and all the changes that occur slowly over time. Patients born with degenerative diseases are acutely aware of the progressive nature of the disease and adapt to each change in their condition. Moreover, for these patients, who have only ever experienced their disease from birth, there is no other state of health to compare to. Therefore, the benchmark for wellbeing or parameters measured by PROMs are altered to account for this, resulting in positive scores for the PROM.

Measuring HRQoL in DMD is affected by confounders, such as the increasing use of a wheelchair, which the patients might view as making life easier because they are able to keep up with their peers. Furthermore, the HRQoL questionnaires don't detect the different disease stages which might also overlay puberty. It is also difficult to compare different estimates of HRQoL on a common index [102], [97]. Cognitive impairment in patients with DMD, which affects approximately a third of patients [103], can manifest as impairments in executive function, working memory, and verbal IQ, all of which could impact accurate self-reporting in QoL assessments [104], [96].

The EuroQoL five-dimension questionnaire (EQ-5D) lacks sensitivity due to the nuances of DMD, as demonstrated in Powell et al. [97]. Nonetheless, Crossnohere et al., 2021 concluded that it can detect differences in broader HRQoL among people with DMD, which indicates that EQ-5D may be appropriate for use in cost-effectiveness analysis [62]. Therefore, as per DMC's guideline, EQ-5D data is prioritised [54], and the health economic model in this application is based on EuroQoL five-dimension questionnaire with 3 levels (EQ-5D-3L) data from Crossnohere et a., 2021 [62].

Table 34 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D	Crossnohere et a., 2021 [62]	Used to inform patient health state utilities and health state costs in the model.

Abbreviations: PODCI = Paediatric Outcomes Data Collection Instrument; PARS III = Personal Adjustment and Role Skills Scale, third edition.

10.1 Presentation of the health-related quality of life

This section is not applicable since the health state utility values in the model are derived from the Crossnohere et al., 2021 study [62] (described in section 10.3).

10.1.1 Study design and measuring instrument

This section is not applicable.

10.1.2 Data collection

This section is not applicable.

Table 35 Pattern of missing data and completion

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
N/A				

10.1.3 HRQoL results

This section is not applicable.

Table 36 HRQoL [instrument 1] summary statistics

	Intervention	Comparator	Intervention vs. comparator
N/A			

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

This section is not applicable since the health state utility values in the model are not from the clinical study VISION-DMD, but instead they are derived from Crossnohere et al., 2021 study [62] in order to focus on EQ-5D data (described in section 10.3).

10.2.1 HSUV calculation

This section is not applicable.

10.2.1.1 Mapping

This section is not applicable.

10.2.2 Disutility calculation

This section is not applicable.

10.2.3 HSUV results

This section is not applicable.

Table 37 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
N/A				

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

Crossnohere et al., 2021 [62] was deemed the most appropriate source of utility values and was used in the model base case. That is because the utilities were measured via EQ-5D-3L, by self or caregiver proxy, depending on the age and cognitive ability of the patient, whereas other sources only relied on proxy measurements and other quality of life instruments.

10.3.1 Study design

Crossnohere et al., 2021 conducted an international, cross-sectional study to assess the appropriateness of the EQ-5D in patients and caregivers affected by DMD. The a priori expectation was that EQ-5D would not be appropriate for economic evaluation. That is because concerns had been raised that EQ-5D does not capture meaningful differences in health status, correlate with disease-specific measures, reflect real health status, exhibit face validity, be accurately interpreted, and be low burden.

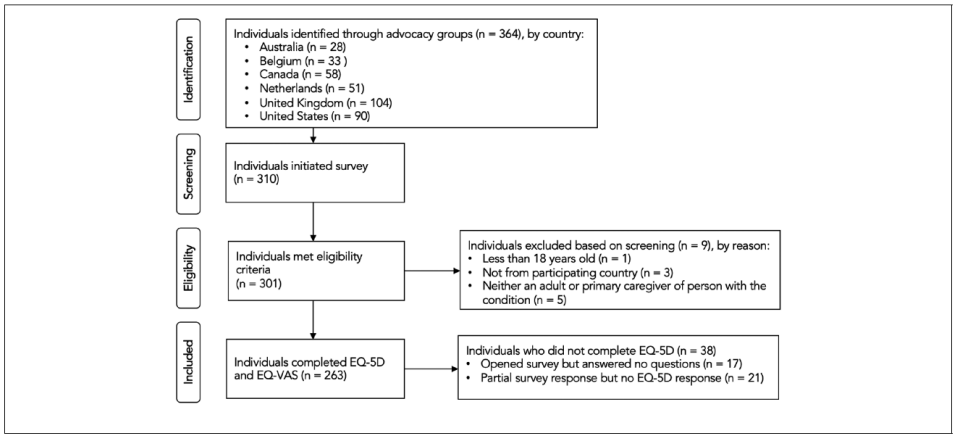
Crossnohere et al., 2021 evaluated the concerns by comparing EQ-5D index scores to other condition-specific functional measures and open- and closed-ended questions. In total, 263 participants (74% response) completed a survey on their experience with DMD. Three-quarters of respondents agreed that EQ-5D measured real health status (74%). Respondents indicated the EQ-5D was easy to understand (86%) and answer (71%). EQ-5D index was higher in ambulatory than non-ambulatory patients (0.60 v. 0.30, P \ 0.001) and was negatively correlated with upper limb impairment (r = 0.61, P \ 0.001). Therefore, the authors concluded that there is support for the appropriateness of EQ-5D to assess health status in DMD.

10.3.2 Data collection

The data collection is depicted in the flow diagram in

Figure 15. Patient groups from 6 countries—Australia, Belgium, Canada, Netherlands, United Kingdom, and United States—recruited adult males with DMD and caregivers of male patients with DMD to participate in an online survey about their experience with Duchenne, including the EQ-5D.

Figure 15 Flow diagram



Source: [62]

Of 364 individuals sent the survey between October 2018 and August 2019, 311 competed screening items, 301 of whom were eligible to participate. A total of 263 respondents went on to complete the survey, including the EQ-5D, and were included in the final analytic sample. Adults with DMD completed the self-reported version of the measure (EQ-5D-3L) while caregivers completed proxy versions (EQ-5D-Proxy1 if patient was 12 years and older or EQ-5D-Y if patient was 11 years and younger). Respondents completed country and language-specific versions of the EQ-5D, which have been validated for cultural equivalence. Responses were converted to an index value ranging from dead (0) to full health (1) based on USA tariffs derived from time trade-off [105]. USA tariffs were used to avoid heterogeneity that would be introduced by using separate country-specific tariffs.

The response rate for the survey was 74%. 263 individuals completed the EQ-5D. However, 38 individuals did not complete the EQ-5D Table 38). Out of that 38, 17 individuals opened the survey but answered no questions, and 21 individuals did not complete EQ-5D but particularly completed the survey (hereby referred to as partial responders). The proportion of respondents to partial responders varied by country (P = 0.02). As compared to partial responders, a lower proportion of respondents were ambulatory (67% v. 37%, P = 0.03), and a higher proportion of respondents were female (0% v. 59%, P = 0.04). No other differences were observed.

Table 38 Pattern of missing data and completion

Time point	HRQoL population N	Missing N (%)	Completion N (%)
	Number of individuals who met eligibility criteria	Number of patients for whom data is missing	Number of patients who completed EQ-5D
October 2018 – August 2019	301	38 (%)	263 (91%)

10.3.3 HRQoL Results

The EQ-5D-3L results for DMD patients from the Crossnohere et al., 2021 study are presented in Table 39.

Table 39 EQ-5D-3L Index across different stages of DMD

Ambulatory class	n	Mean (SD)	P Value[a]
Early ambulatory	71	0.65 (0.17)	<0.001
Late ambulatory	31	0.49 (0.23)	
Early nonambulatory	111	0.31 (0.20)	
Late nonambulatory	50	0.26 (0.16)	

[a] Within-group comparisons using x2 tests. Source: [62]

10.3.4 HSUV and disutility results

The health state utility values (measured via EQ-5D-3L) used in the model are based on Crossnohere et al., 2021 [62] and described in Table 40. These are age-adjusted from the age of 18 according to the Danish population, as per DMC guidelines [73]. Utility decrements were applied to all acute events, AESI and comorbidities experienced by patients for DMD. An overview of disutilities is presented in Table 40. All disutilities were sourced from relevant published literature and informed by clinical opinion where data were not available. The base case in the model is based on moderate/severe AESIs. Given the paucity of utility data by AE severity, a proxy approach was used for mild AESI disutilities by applying 25% of the disutility for moderate/severe AESI.

Since disutilities of behavioural difficulties and stunted growth are impactful factors in the analysis, a more detailed explanation of the choice and sources of the disutility values is provided below.

The study used to derive the disutility for behavioural issues is based on a time trade-off study conducted in a Dutch population [65]; 529 people were asked to value 10 to 11 health state scenarios in epilepsy. One of the measured health state was the “experience of side effects” from antiepileptic drugs. The magnitude was categorized into three levels; no or mild, moderate and severe side-effects. The results showed that these side-effects have a significant impact on QoL. The regression coefficient -0.061 was found for the side-effects from antiepileptics, and this decrement was used for the calculation of disutilities in the health economic model. Aligned with the study, the decrement was coded as *2 to represent severe side effects. The study results have been used and accepted in NICE evaluations for a pediatric population with Lennox–Gastaut syndrome [106] and, after careful consideration and consultation with clinicians and patients, NICE also accepted it in their evaluation for vamorolone in the treatment of DMD [107].

The disutility for stunted growth was sourced from the NICE evaluation of “Metreleptin for treating lipodystrophy” [66]. In this appraisal, the company applied a decrement of 0.056 for impaired physical appearance, derived from a discrete choice experiment,

alongside other decrements intended to capture aspects of lipodystrophy not previously reflected. After careful consideration NICE accepted this disutility in their evaluation for vamorolone in the treatment of DMD [107].

AEs were applied per cycle according to incidence data. Durations of all acute events and AESI were taken from treatment-specific VISION-DMD data where available (all acute events, weight gain, cushingoid and immune suppression), reflective of the average duration seen in the trial for each respective AE. The disutility associated with each event was then calculated based on its duration to apply a one-off QALY loss for each event occurrence in the model. The formula for QALY loss = disutility value x duration or disutility / 365.25 (days per year, taking leap year into account).

Caregiver utilities are not applied in the model base case [61]. In addition to general caregiver utilities, a caregiver disutility for behavioural issues is included in the model [72] but will only be applied if the setting for caregiver utilities is also applied. See Appendix L for scenario analysis.

Table 40 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Health state utility values				
Early ambulatory	0.65 (N/R)	EQ-5D-3L	US	EQ-5D-3L data was collected for DMD patients in Crossnohere et al., 2021 [62]. Since Santhera Pharmaceuticals did not have access to individual patient data from that study, it was not possible to calculate utility values based on Danish preference weights.
Late ambulatory	0.49 (N/R)	EQ-5D-3L	US	
Transfer	0.49 (N/R)	EQ-5D-3L	US	
HTMF, no ventilation	0.31 (N/R)	EQ-5D-3L	US	
No HTMF, no ventilation	0.31 (N/R)	EQ-5D-3L	US	
HTMF, night-time ventilation	0.26 (N/R)	EQ-5D-3L	US	
No HTMF, night-time ventilation	0.26 (N/R)	EQ-5D-3L	US	
Full-time ventilation	0.26 (N/R)	EQ-5D-3L	US	
Disutilities from adverse events of special interest				

Weight gain	-0.050 (N/R)	N/A, utility assumed in source	N/A, utility assumed in source	Disutility: value based on ICER submissions for DMD [64] Duration for vamorolone and glucocorticoids: [redacted] based on VISION-DMD [74].
Behavioural issues	-0.120 (N/R)	EQ-5D	UK, Netherlands	Disutility: value calculated for behaviour issues, specifically for irritability and aggression, based on a NICE submission in a paediatric population [106]. The value is based on [65], where an event regression coefficient of -0.061 for the 'experience of side effects' in epilepsy was reported. The coding used for severe side effects was 0.061*2. This disutility has later also been accepted by NICE in DMD [107] . Duration for vamorolone and glucocorticoids: [redacted] assumed.
Cushingoid effects	-0.056 (N/R)	EQ-5D-3L	UK	Disutility: value from a previous NICE submission [66] for impaired physical appearance. This value was based on several conditions including excessive facial hair, skeletal facial features, severe body asymmetry. This is seen to adequately capture cushingoid facial features. Duration for vamorolone: [redacted] based on VISION-DMD [74]. Duration for glucocorticoids: [redacted] based on VISION-DMD [74].
Immune supressed/infection	-0.142 (N/R)	EQ-5D	UK	Disutility: value from [67]. Upper respiratory tract infection (URTI) was the most common infection which has been assumed to represent this event. Duration for vamorolone: [redacted] based on VISION-DMD [74]. Duration for glucocorticoids: [redacted] based on VISION-DMD [74].
Gastrointestinal symptoms	-0.02 (N/R)	EQ-5D-3L	Denmark	Disutility: EQ-5D data based on chronic conditions and health risks [68]. Duration for vamorolone and glucocorticoids: [redacted] [74].

Diabetes	-0.03 (N/R)	EQ-5D-3L	Denmark	Disutility: EQ-5D data based on chronic conditions and health risks [68]. Duration for vamorolone and glucocorticoids: [redacted] [74].
Skin/Hair change	-0.056 (N/R)	EQ-5D-3L	UK	Disutility: Value from a previous NICE submission [66] for impaired physical appearance. This value was based on several conditions including excessive facial hair, skeletal facial features, severe body asymmetry. This captures hirsutism arising during skin and hair AE for those with DMD. Duration for vamorolone and glucocorticoids: [redacted] [74].
Stunted growth	-0.056 (N/R)	EQ-5D-3L	UK	Disutility: Value is from a previous NICE submission [66] for impaired physical appearance. This value was based on several conditions including excessive facial hair, skeletal facial features, severe body asymmetry.[a] This disutility has been also accepted later by NICE in DMD [107] . Duration for vamorolone and glucocorticoids: [redacted] conservatively based on input from a Danish clinical expert that the negative impact of stunted growth would last the patient's lifetime [35].
Disutilities from acute events				
Diarrhoea	-0.047 (N/R)	EQ-5D	UK	Disutility: sourced diarrhoea disutility from [67]. Duration for vamorolone: [redacted] based on VISION-DMD [74]. Duration for glucocorticoids: [redacted] based on VISION-DMD [74].
Vomiting	-0.095 (-0.05, 0.24)	EQ-5D-3L	Japan	Disutility: sourced vomiting disutility from [69] Duration for vamorolone: [redacted] based on VISION-DMD [74]. Duration for glucocorticoids: [redacted] based on VISION-DMD [74].

Pyrexia	-0.0297 (N/R)	EQ-5D	UK	Disutility: sourced pyrexia disutility from [67]. Duration for vamorolone: [redacted] based on VISION-DMD [74]. Duration for glucocorticoids: [redacted] based on VISION-DMD [74].
Cough	-0.046 (N/R)	EQ-5D	UK	Disutility: Sourced cough disutility from [70]. Duration for vamorolone: [redacted] based on VISION-DMD [74]. Duration for glucocorticoids: [redacted] based on VISION-DMD [74].
Disutilities from comorbidities				
Spinal fusion surgery	-0.07 (N/R)	EQ-5D	UK	Disutility: value based on skeletal-related events, specifying the disutility obtained specifically from bone-related surgery [63]. Duration for vamorolone and glucocorticoids: [redacted]. This is a conservation assumption, since loss of motor function has a lifetime impact. Additionally, disutility associated with sacrum joints and back pain because of spinal surgery would result in a further reduction in QoL, which could not be incorporated in the model.
Spinal vertebral fractures	-0.05 (N/R)	EQ-5D-3L	Australia, Canada, UK, USA	Disutility: values for spinal vertebral fractures and 'other fractures' (patella, tibia, fibula, ankle and femur) were sourced from [71]. The study looked at HRQoL outcomes following injury in childhood with a long-term follow-up of 24 months. A disutility for vertebral column fractures was used, and an average of fractures for patella, tibia, fibula or ankle and fractures of the femur was applied for the other fractures' disutility. Duration for vamorolone and glucocorticoids: [redacted] based on clinical input [87].
Non-vertebral fractures	-0.065 (N/R)	EQ-5D-3L	Australia, Canada, UK, USA	

a. As the rate of stunted growth is dependent on both the treatment and dosage of treatment that a patient receives, the disutility accrued by growth stunting cannot be assumed as sufficiently captured within the health state utilities alone. Subsequently, the disutility for impaired physical appearance was applied within the model utilising a disutility for short stature obtained from obtained from a NICE submission for patients with atypical

haemolytic uraemic syndrome, which was deemed the most appropriate source by UK clinical experts [87] [66].
Abbreviations: AE = Adverse event; HTMF = hand-to-mouth function; ICER = Incremental cost-effectiveness ratio; N/R = No result; NICE = National Institute for Health and Care Excellence; UK = Unite Kingdom; USA = United States of America; QoL = Quality of life; EQ-5D-3L = EuroQoL five-dimension questionnaire (3 levels)

Table 41 Overview of literature-based health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Early ambulatory				
Crossnohere et al., 2021	0.65 (N/R)	EQ-5D-3L	US	EQ-5D-3L data was collected for DMD patients in Crossnohere et al., 2021 [62]. Since Santhera Pharmaceuticals did not have access to individual patient data from that study, it was not possible to calculate utility values based on Danish preference weights.
Landfeldt et al., 2017	0.70 (N/R)	EQ-5D-3L	UK	EQ-5D-3L data was collected for DMD patients in Landfeldt et al., 2017 [61]. Since Santhera Pharmaceuticals did not have access to individual patient data from that study, it was not possible to calculate utility values based on Danish preference weights.
Late ambulatory				
Crossnohere et al., 2021	0.49 (N/R)	EQ-5D-3L	US	Please see comment for Early ambulatory
Landfeldt et al., 2017	0.61 (N/R)	EQ-5D-3L	UK	Please see comment for Early ambulatory
Early nonambulatory				
Crossnohere et al., 2021	0.31 (N/R)	EQ-5D-3L	US	Please see comment for Early ambulatory
Landfeldt et al., 2017	0.22 (N/R)	EQ-5D-3L	UK	Please see comment for Early ambulatory
Late nonambulatory				

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Crossnohere et al., 2021	0.26 (N/R)	EQ-5D-3L	US	Please see comment for Early ambulatory
Landfeldt et al., 2017	0.15 (N/R)	EQ-5D-3L	UK	Please see comment for Early ambulatory

11. Resource use and associated costs

11.1 Medicines - intervention and comparator

An overview of medicines used in the model is shown in Table 42.

Table 42 Medicines used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Vamorolone	6 mg/kg [60]	100%	Daily	No
Prednisolone	0.75 mg/kg [10]	100%	Daily	No
Deflazacort	0.90 mg/kg [10]	100% [35]	Daily	No

In the base case, it is assumed that starting treatment is administered at the recommended dosages of vamorolone, prednisolone and deflazacort. . As described in section 8.4, after 6 months, xxx of vamorolone patients down-titrate to 4 mg/kg. Prednisolone and deflazacort down-titration is applied over time according to CINRG data, which is based on the average dose of each treatment by age. For prednisolone and deflazacort patients who down-titrate, this corresponds to a xxx reduction in efficacy. This is based on the strong body of evidence from the literature which indicates that that sub-optimal doses from down-titrating glucocorticoids by reducing the daily dose or using intermittent dosing leads to loss of efficacy [5, 15, 16]. The Danish list price of vamorolone is 41,047 DKK per pack. The pack price of prednisolone is 109 DKK per pack and the pack price of deflazacort is 845 DKK per pack.

Packages of medicine

There is only one pack available of vamorolone [60] and deflazacort [53]. Prednisolone is available in multiple pack sizes as shown in section 3.5 (Table 4) [49], [50], [51]. In the model, the pack size used is 100 tablets at 25 mg per tablet.

Treatment duration

Treatment with vamorolone is chronic and recommended for DMD patients aged four and above [60]. Treatment with prednisolone and deflazacort is also chronic, and recommended for both ambulatory and non-ambulatory DMD patients [39]. In the model, it is assumed that patients are treated until death. This is based on Danish clinical input that prednisolone and deflazacort is used until non-tolerance/death [108].

Medicine waste

No medical waste has been assumed with vamorolone because after opening the glass bottle containing the oral suspension of vamorolone, the suspension can be used within 3 months [60]. No medical waste has also been assumed with prednisolone and deflazacort. Prednisolone and deflazacort are administered as oral tablets [49-51, 53], and in Denmark the treatment with them is chronic and until non-tolerance [108].

11.2 Medicines– co-administration

This section is not applicable.

11.3 Administration costs

Administration costs are assumed to be zero, because vamorolone, prednisolone and deflazacort are self-administered orally. Therefore, administration costs have not been included in the model and this section is not applicable.

Table 43 Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
N/A				

11.4 Disease management costs

Health state costs (comprising direct medical costs) were applied in the model for vamorolone and prednisolone/deflazacort. The same annual cost was applied for vamorolone and prednisolone/deflazacort, with the cost per model cycle determined by proportion of patients in each treatment arm in each health state at any given time. The costs were sourced from the Landfeldt et al., 2017 publication [61], as it was used in a previous HTA for ataluren in DMD (SMC2327) and HST22 [109, 110]. The direct medical costs available in Landfeldt et al., 2017 were UK costs, therefore these were converted to Danish krone (DKK) in January 2025 to derive equivalent Danish costs. These costs were used given there was no cost data by disease state for Denmark (or any Nordic country), and this was required in order to align with the model.

These costs were specific to the resource use applied in each health state, which ensures consistency with the health utilities used in the model. The costs, which are from 2015, were inflated to the latest 2024 values via the Danmarks Nationalbank CPI index.

Table 44 Disease management costs used in the model

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Early ambulatory	Annual cost	110,874	N/A	Landfeldt et al., 2017 [61]
Late ambulatory	Annual cost	116,278	N/A	Landfeldt et al., 2017 [61]
Transfer	Annual cost	171,351	N/A	Landfeldt et al., 2017 [61]
HTMF, no ventilator	Annual cost	171,351	N/A	Landfeldt et al., 2017 [61]
No HTMF, no ventilator	Annual cost	286,694	N/A	Landfeldt et al., 2017 [61]
HTMF, night ventilator	Annual cost	329,506	N/A	Landfeldt et al., 2017 [61]
No HTMF, night vent	Annual cost	329,506	N/A	Landfeldt et al., 2017 [61]
Full time ventilation	Annual cost	378,137	N/A	Landfeldt et al., 2017 [61]

11.5 Costs associated with management of adverse events

Costs for spinal vertebral fractures and other fractures were included in the model and applied to those patients who receive fractures on a per cycle basis. To capture the 'other fractures' cost, an average of all fractures was taken. This approach was implemented to reflect the difficulties associated with surgery for DMD patients. For patients who receive a fracture, a one-off dual-energy X-ray absorptiometry (DEXA) scan cost is applied.

The cost implications from experiencing scoliosis were captured through spinal fusion surgery events and applied as a one-off cost within the model. Spinal fusion surgery follow-up costs were applied twice (representing two follow-ups) for patients who undergo spinal fusion surgery.

Table 45 Cost associated with management of adverse events

	DRG code	Unit cost/DRG tariff [DKK]
Vertebral fracture	08MA16	63,024

	DRG code	Unit cost/DRG tariff [DKK]
Other fractures	08MA02	46,114
Spinal surgery – elective	01MP01	224,031
Spinal surgery follow-up – elective	08MA06	38,641
Fracture DEXA scan	36PR08	3,189

11.6 Subsequent treatment costs

This section is not applicable. Subsequent treatment costs are not included in the model. That is because it is assumed that treatment with prednisolone and deflazacort are until death/non-tolerance, based on Danish clinical input [108].

Table 46 Medicines of subsequent treatments

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
N/A				

11.7 Patient costs

Transport and time spent cost are not included in the model base case given treatment can be administered orally and not in the hospital setting where monitoring of treatment would ordinarily be required.

Table 47 Patient costs used in the model

Activity	Time spent [minutes, hours, days]
Activity	N/A

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

This section is not applicable since palliative care costs associated with the intervention and comparator are assumed to be the same, thus these costs are not included in the model.

12. Results

12.1 Base case overview

An overview of the base case is provided in Table 48. The base case model includes the option to compare vamorolone versus either prednisolone or deflazacort, separately. Therefore, relevant base case information related to both comparators is included in Table 48.

Table 48 Base case overview

Feature	Description
Comparator	Prednisolone Deflazacort
Type of model	Markov model
Time horizon	50 years (life time)
Treatment line	1st line. Subsequent treatment lines not included. If a patient stops treatment while still alive, they are assumed to receive no treatment until death.
Measurement and valuation of health effects	Health-related quality of life measured with EQ-5D-5L in Crossnohere et al., 2021 [62]. Since Santhera Pharmaceuticals did not have access to individual patient data from that study, it was not possible to calculate utility values based on Danish preference weights.
Costs included	Medicine costs, disease management costs, costs of adverse and acute events
Dosage of medicine	Starting dose is based on weight for vamorolone and prednisolone/deflazacort. Some patients down-titrate from their starting dose, given this happens in clinical practice
Average time on treatment	Vamorolone [redacted]; Prednisolone: [redacted]; Deflazacort: [redacted]
Parametric function for PFS	N/A
Parametric function for OS	N/A
Inclusion of waste	No medicine waste assumed (see section 11.1)

12.1.1 Base case results

The base case results for vamorolone versus prednisolone are presented in Table 49. The base case results for vamorolone versus deflazacort are presented in Table 50.

Table 49 Base case results, discounted estimates (vs. prednisolone)

	Vamorolone	Prednisolone	Difference
Drug acquisition costs (DKK)	[redacted]	[redacted]	[redacted]
Drug administration costs (DKK)	[redacted]	[redacted]	[redacted]
Monitoring (health state) costs (DKK)	[redacted]	[redacted]	[redacted]
Costs associated with management of adverse & acute events (DKK)	[redacted]	[redacted]	[redacted]
Subsequent treatment costs (DKK)	[redacted]	[redacted]	[redacted]
Societal costs (DKK)	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]
Life years gained (Early Amb)	[redacted]	[redacted]	[redacted]
Life years gained (Late Amb)	[redacted]	[redacted]	[redacted]
Life years gained (Transfer)	[redacted]	[redacted]	[redacted]
Life years gained (HTMF no vent)	[redacted]	[redacted]	[redacted]
Life years gained (No HTMF no vent)	[redacted]	[redacted]	[redacted]
Life years gained (HTMF night vent)	[redacted]	[redacted]	[redacted]
Life years gained (No HTMF night vent)	[redacted]	[redacted]	[redacted]

	Vamorolone	Prednisolone	Difference
Life years gained (Full vent)	Xxxxxxx	Xxxxx	Xxxx
Total life years	Xxxxxx	Xxxxx	Xxxx
QALYs (Early Amb)	Xxxxx	Xxxx	Xxxx
QALYs (Late Amb)	Xxxx	Xxx	Xxxx
QALYs (Transfer)	Xxxx	Xxxx	Xxxx
QALYs (HTMF no vent)	Xxxxx	Xxxx	Xxxx
QALYs (No HTMF no vent)	Xxxxx	Xxxx	Xxxx
QALYs (HTMF night vent)	Xxxx	Xxx	xxxx
QALYs (No HTMF night vent)	Xxxx	Xxxx	Xxxx
QALYs (Full vent)	Xxxxx	Xxxx	Xxxx
QALYs (adverse reactions)	Xxxxx	Xxxx	Xxxx
QALYs (acute events)	Xxxx	Xxxx	Xxxx
Total QALYs	Xxxxx	Xxxx	Xxxx
Incremental costs per life year gained		xxxxxxxx	
Incremental cost per QALY gained (ICER)		xxxxxxxxxxxxxx	

Table 50 Base case results, discounted estimates (vs. deflazacort)

	Vamorolone	Deflazacort	Difference
Drug acquisition costs (DKK)	Xxxxxxxxxx	Xxxxxxxxxx	Xxxxxxxxx
Drug administration costs (DKK)	Xx	x	Xxxx
Monitoring (health state) costs (DKK)	Xxxxxxxxx	Xxxxxxx	Xxxxx

	Vamorolone	Deflazacort	Difference
Costs associated with management of adverse & acute events (DKK)	Xxxxxxxxx	Xxxxxxxxxx	xxxxxxxxx
Subsequent treatment costs (DKK)	Xx	X	Xx
Societal costs (DKK)	X	X	Xxx
Total costs	Xxxxxxxxx	Xxxxxxxxx	Xxxxxxxxx
Life years gained (Early Amb)	Xxxxx	Xxxxxx	Xxxxx
Life years gained (Late Amb)	Xxxx	Xxxxxx	xxxxxxx
Life years gained (Transfer)	Xxx	Xxxx	Xxxx
Life years gained (HTMF no vent)	Xxxxx	Xxxx	Xxxxx
Life years gained (No HTMF no vent)	Xxxx	Xxxx	Xxxx
Life years gained (HTMF night vent)	Xxxx	Xxxx	Xxxx
Life years gained (No HTMF night vent)	Xxxx	Xxxx	Xxxx
Life years gained (Full vent)	Xxxxx	Xxxxx	Xxxxx
Total life years	Xxxxxx	Xxxxx	Xxxx
QALYs (Early Amb)	Xxxx	Xxxx	Xxx
QALYs (Late Amb)	Xxxxx	Xxxx	Xxx
QALYs (Transfer)	Xxxx	Xxxx	Xxxx
QALYs (HTMF no vent)	Xxxx	Xxx	Xxxx
QALYs (No HTMF no vent)	Xxxx	Xxx	xxxx

	Vamorolone	Deflazacort	Difference
QALYs (HTMF night vent)	[redacted]	[redacted]	[redacted]
QALYs (No HTMF night vent)	[redacted]	[redacted]	[redacted]
QALYs (Full vent)	[redacted]	[redacted]	[redacted]
QALYs (adverse reactions)	[redacted]	[redacted]	[redacted]
QALYs (acute events)	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
Incremental costs per life year gained		[redacted]	
Incremental cost per QALY gained (ICER)		[redacted]	

12.2 Sensitivity analyses

12.2.1 Deterministic sensitivity analyses

The results from the one-way sensitivity analyses are presented below as tornado diagrams versus prednisolone (Table 51) and deflazacort (Table 52). [redacted] The top three influential parameters for prednisolone and deflazacort are presented in more detail in Table 51 and Table 52 below.

For scenario analyses with [redacted] and [redacted] see Appendix L

Table 51 One-way sensitivity analyses results (versus prednisolone)

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 52 One-way sensitivity analyses results (versus deflazacort)

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 16 [redacted]

[redacted]

Figure 17 [redacted]

[redacted]

12.2.2 Probabilistic sensitivity analyses

PSA was undertaken comparing to each of prednisolone and deflazacort, separately. In both cases, the PSA was run for 1,000 simulations. An incremental cost-effectiveness plane (ICEP) scatter plot and cost-effectiveness acceptability curve (CEAC) were produced to graphically illustrate the level of variability and uncertainty in the results.

In both cases, the ICEP (Figure 17 – versus prednisolone; Figure 19 – versus deflazacort) shows that all iterations maintain the same hierarchy of results with vamorolone constantly generating more costs and QALYs than prednisolone and deflazacort. The results lie on the north-eastern quadrant of the cost/QALY graph, meaning that vamorolone is more costly than prednisolone and deflazacort but also more efficacious. The CEAC (**Error! Reference source not found.** – versus prednisolone; **Error! Reference source not found.** – versus deflazacort) shows that at a WTP threshold of [redacted] probability of being cost-effective versus prednisolone. At WTP threshold of [redacted] probability of being cost effective versus deflazacort.

Figure 18 [redacted]

[redacted]

Figure 19 [redacted]

[redacted]

Figure 20 [redacted]

[redacted]

Figure 21 [redacted]

[redacted]

Budget impact analysis

Number of patients (including assumptions of market share)

It is estimated that the total patient population for all years will be [redacted], which is estimated based on the prevalence of patients in 2021 from a DMD registry study [28]. [redacted]

Table 53 Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which, new patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prednisolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			Non-recommendation		
Vamorolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which, new patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prednisolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Budget impact

Table 54 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]

13. List of experts

[redacted]

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Appendix A. Main characteristics of studies included

Table 55 Main characteristic of studies included – VISION-DMD (VBP15-004)

Trial name: VISION-DMD	**NCT number: NCT03439670**
Objective	To evaluate the efficacy and safety of vamorolone administered orally at daily doses of 2.0 mg/kg/day and 6.0 mg/kg/day vs prednisone 0.75 mg/kg/day and placebo over 24 weeks with a cross over of the prednisone and placebo arms to the two vamorolone doses for a further 24 weeks, making the total study length 48 weeks in ambulant boys aged 4 to <7 years with DMD.
Publications – title, author, journal, year	Efficacy and Safety of Vamorolone vs Placebo and Prednisone Among Boys With Duchenne Muscular Dystrophy, Guglieri M. et al., JAMA Neurology, 2022 AND Dang et al., 2024
Study type and design	Phase IIb, randomized, double-blind, parallel group study on the efficacy and safety of vamorolone vs placebo and prednisone where study objects were randomized 2:2:1:1:1:1 and stratified by age at study entry (<6 years and ≥6 years). In Period 1 (Day 1 to Week 24), subjects were randomized to 1 of 4 groups: placebo, vamorolone 2.0 mg/kg/day, vamorolone 6.0 mg/kg/day, and prednisone 0.75 mg/kg/day. After a 4-week transition period, (Week 25 to Week 28), in Period 2 (Week 28 + 1 day to Week 48), both placebo- and prednisone-treated subjects crossed over to vamorolone (2.0 mg/kg/day or 6.0 mg/kg/day).
Sample size (n)	*121*
Main inclusion criteria	• Males aged ≥4 to <7 years at enrolment, with a *DMD* gene loss-of-function variation or lack of muscle dystrophin • Not previously treated with glucocorticoids • Body weight >13.0 kg and ≤39.9 kg at the screening visit • Able to walk independently without assistive devices • Able to complete TTSTAND without assistance in <10 seconds at the screening visit
Main exclusion criteria	• Current or previous treatment with oral glucocorticoids or other immunosuppressive agents • Usage of mineralocorticoid receptor agents (i.e., spironolactone, eplerenone, canrenone, prorenone, mexrenone) within 4 weeks prior to the first dose of study medication • Usage of Idebenone at least 4 weeks prior to first dose of study drug

Trial name: VISION-DMD	NCT number: NCT03439670
	• Usage of any approved medications or herbal remedies that could impact strength and function (including, but not limited to, Co-enzyme Q10, creatine) at least 4 weeks before the first dose of study drug • Current or history of major renal or hepatic impairment, diabetes mellitus, immunosuppression, chronic systemic fungal or viral infection • Medications indicated for the treatment of DMD, including Exondys51 and Translarna, at least 3 months prior to first dose of study drug • Any investigational medications other than vamorolone at least 3 months before the first dose of study drug • Current or history of major renal or hepatic impairment, diabetes mellitus or immunosuppression • History of primary hyperaldosteronism • Evidence of symptomatic cardiomyopathy (note: asymptomatic cardiomyopathy was not exclusionary) • Severe behavioural or cognitive problems that precluded participation in the study
Intervention	Vamorolone administered orally at daily doses of 2.0 mg/kg/day and 6.0 mg/kg/day.
Comparator(s)	• Prednisone administered orally at a daily dose of 0.75 mg/kg/day • Placebo administered orally
Follow-up time	Follow-up time: 48 weeks • Period 1 (day 1 to Week 24): prednisone and placebo-controlled • 4-week Transition Period (Week 25 to Week 28): for subjects who received either prednisone or placebo • Period 2 (Week 28 + 1 day to Week 48): prednisone- and placebo-treated patients were crossed over to vamorolone for 20 Week Study start: June 2018; completion: September 2019)
Is the study used in the health economic model?	Yes - wherever feasible, clinical inputs for the model were sourced from VISION-DMD for vamorolone and prednisone. Note that EQ-5D data was sourced from the Landfeldt et al. (2023) study [111].
Primary, secondary and exploratory endpoints	Efficacy endpoints included in this application: • TTSTAND velocity (primary endpoint) • TTCLIMB velocity • TTRW velocity

Trial name: VISION-DMD	NCT number: NCT03439670
	• NSAA • 6MWT Safety outcomes included in the application: • AEs • Height • Bone biomarkers (serum osteocalcin, P1NP and CTX) • Behavioural changes (PARS III)
Method of analysis	The change from baseline was calculated from baseline (first study visit) to week 24 (last study visit of the study Period 1)). Descriptive statistics are based on observed cases (without multiple imputation). The LSM estimates were derived from a REML - based MMRM model with enrollment stratification age group (4-5 years; 6-<7 years), treatment (vamorolone 2.0 mg/kg/day, vamorolone 6.0 mg/kg/day, prednisone 0.75 mg/kg/day, and placebo), week, baseline response, and the treatment-by-week interaction. Study week was included in the model as a categorical variable (Weeks 6, 12, and 24) along with the treatment-by-week interaction. An unstructured covariance structure was and the Kenward-Roger approximation was used to estimate denominator degrees of freedom.
Subgroup analyses	N/A
Other relevant information	*N/A*

Abbreviations: AEs = Adverse events; 6MWT = 6-minute walk test; NSAA = North Star Ambulatory Assessment; TTRW = Time to run/walk 10m; TTSTAND = Time to stand from supine; kg = kilogram; mg = milligram; MMRM = mixed model for repeated measures; N/A = Not applicable; LSM = least squares mean; EQ-5D = EuroQol five dimension questionnaire; PARS III = Psychosocial Adjustment and Role Skills Scale third edition; P1NP = Procollagen type 1 N-terminal propeptide; CTX = C-terminal telopeptide of type 1 collagen.

Table 56 Main characteristic of studies included – FOR-DMD

Trial name: FOR-DMD	NCT number: NCT01603407
Objective	To compare efficacy and safety of three corticosteroid regimens (daily prednisone, intermittent prednisone and daily deflazacort) in boys with Duchenne muscular dystrophy.
Publications – title, author, journal, year	Effect of Different Corticosteroid Dosing Regimens on Clinical Outcomes in Boys With Duchenne Muscular Dystrophy: A Randomized Clinical Trial, Guglieri M. et al., JAMA Network, 2022
Study type and design	Phase III, double-blind, parallel group, randomized clinical study on the efficacy and safety of 3 glucocorticoid regimens (daily prednisone, intermittent prednisone and daily deflazacort).

Trial name: FOR-DMD	NCT number: NCT01603407
Sample size (n)	*196*
Main inclusion criteria	• Confirmed diagnosis of DMD defined as: male with clinical signs compatible with DMD and a confirmed DMD mutation in the dystrophin gene • Age ≥ 4 years and < 8 years • Ability to rise independently from floor, from supine to standing, as assessed at screening visit • Ability to maintain reproducible FVC measurements
Main exclusion criteria	• History of major renal or hepatic impairment, immunosuppression or other contraindications to corticosteroid therapy • History of chronic systemic fungal or viral infections. Acute bacterial infection (including tuberculosis) would exclude from enrolment until the infection had been appropriately treated and resolved • Diabetes mellitus • Idiopathic hypercalciuria • Lack of chicken pox immunity and refusal to undergo immunization • Evidence of symptomatic cardiomyopathy at screening assessment • Current or previous treatment (greater than four consecutive weeks of oral therapy) with corticosteroids or other immunosuppressive treatments for DMD or other recurrent indications (e.g., asthma) • Inability to take tablets, as assessed by the site investigator by the end of the screening period • Allergy/sensitivity to study drugs or their formulations including lactose and/or sucrose intolerance • Severe behavioural problems, including severe autism • Previous or ongoing medical condition, medical history, physical findings or laboratory abnormalities that could affect safety, make it unlikely that treatment and follow up will be correctly completed or impair the assessment of study results, in the judgment of the site investigator • Weight of less than 13.0 kg • Exposure to any investigational drug currently or within 3 months prior to start of study treatment
Intervention	• Prednisone 0.75 mg/kg/day • Intermittent prednisone 0.75 mg/kg/day (10 days on, 10 days off) • Deflazacort 0.90 mg/kg/day

Trial name: FOR-DMD	NCT number: NCT01603407
Comparator(s)	N/A
Follow-up time	36 months (study start: January 2013, completion: November 2019)
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	Efficacy endpoints included in this application: • TTRF velocity (equivalent to TTSTAND velocity) [5] Safety endpoints included in the application: • AE • Height
Method of analysis	Time to rise from the floor (TTRF) velocity: The adjusted group mean for each corticosteroid regimen and the differences between the regimens were obtained from a repeated-measures analysis of covariance model with terms for treatment group, country, baseline weight-band dosage, the baseline value of the outcome variable, time (treated as a categorical variable), and interaction terms for the baseline value of the outcome variable × time and for treatment group × time [5].
Subgroup analyses	N/A
Other relevant information	*N/A*

Abbreviations: AE = Adverse event; FVC = Forced Vital Capacity; kg = kilogram; mg = milligram; MMRM = mixed model for repeated measures; N/A = Not applicable; TTRF = Time taken to rise from the floor. Source [5] – *including the study protocol published as a supplement to the original article.*

Appendix B. Efficacy results per study

Results per study

The tables below present relevant efficacy outcomes for all studies included in the application, regardless of whether they have been used in the health economic model.

Table 57 VISION-DMD results at week 24: vamorolone versus placebo

Results of VISION-DMD (NCT03439670)												
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	LSM (SE) change from baseline	LSM difference (SE)	95% CI	*P* value	Difference	95% CI	*P* value		
TTSTAND velocity [57]	Vamolorone 6.0 mg/kg/day	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]							[redacted]
TTRW velocity	Vamolorone 6.0 mg/kg/day	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]								[redacted]

6MWT	Vamolorone 6.0 mg/kg/day	[redacted]											
	Placebo	[redacted]											
TTCLIMB velocity	Vamolorone 6.0 mg/kg/day	[redacted]											
	Placebo	[redacted]											
NSAA	Vamolorone 6.0 mg/kg/day	[redacted]											
	Placebo	[redacted]											

[a] The LSM estimates were derived from a REML - based MMRM model with with multiple imputation based on the missing at random imputation, enrollment stratification age group (4-5 years; 6-<7 years), treatment (vamorolone 2.0 mg/kg/day, vamorolone 6.0 mg/kg/day, prednisone 0.75 mg/kg/day, and placebo), week, baseline response, and the treatment-by-week interaction. Study week was included in the model as a categorical variable (Weeks 6, 12, and 24) along with the treatment-by-week interaction. An unstructured covariance structure was and the Kenward-Roger approximation was used to estimate denominator degrees of freedom.
Abbreviations: CI = Confidence interval; LSM = Least squares mean; TTSTAND = Time to stand test; TTCLIMB = Time to climb 4 steps; TTRW = Time to Run/Walk 10 meters; 6MWT = 6 Minute Walk Test; NSAA=North Star Ambulatory Assessment; REML = Restricted maximum likelihood; SE = Standard error; MMRM = Mixed models for repeated measures.

Table 58 VISION-DMD results at week 24: vamorolone versus prednisone

Results of VISION-DMD (NCT03439670)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	LSM (SE) change from baseline	LSM difference (SE)	95% CI	*P* value	Difference	95% CI	*P* value		
TTSTAND	Vamolorone 6mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Prednisone	[redacted]	[redacted]								[redacted]
TTRW velocity	Vamolorone 6.0 mg/kg/day	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Results of VISION-DMD (NCT03439670)												
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	LSM (SE) change from baseline	LSM difference (SE)	95% CI	*P* value	Difference	95% CI	*P* value		
										[redacted]	
	Prednisone	[redacted]	[redacted]							[redacted]	
6MWT	Vamolorone 6.0 mg/kg/day	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Prednisone	[redacted]	[redacted]							[redacted]	

Results of VISION-DMD (NCT03439670)												
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References	
Outcome	Study arm	N	LSM (SE) change from baseline	LSM difference (SE)	95% CI	*P* value	Difference	95% CI	*P* value			
TTCLIMB velocity	Vamolorone 6.0 mg/kg/day	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
	Prednisone	[redacted]	[redacted]							[redacted]		
NSAA	Vamolorone 6.0 mg/kg/day	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
	Prednisone	[redacted]	[redacted]							[redacted]		

[a] The LSM estimates were derived from a REML - based MMRM model with multiple imputation based on the missing at random imputation, enrolment stratification age group (4-5 years; 6-<7 years), treatment (vamorolone 2.0 mg/kg/day, vamorolone 6.0 mg/kg/day, prednisone 0.75 mg/kg/day, and placebo), week, baseline response, and the treatment-by-week interaction. Study week was included in the model as a categorical variable (Weeks 6, 12, and 24) along with the treatment-by-week interaction. An unstructured covariance structure was and the Kenward-Roger approximation was used to estimate denominator degrees of freedom.
Abbreviations: CI = Confidence interval; LSM = Least squares mean; TTSTAND = Time to stand test; TTCLIMB = Time to climb 4 steps; TTRW = Time to Run/Walk 10 meters; 6MWT = 6 Minute Walk Test; NSAA=North Star Ambulatory Assessment; REML = Restricted maximum likelihood; SE = Standard error; MMRM = Mixed models for repeated measures; N/A = Not applicable.

Table 59 FOR-DMD results at month 36

Results of FOR-DMD (NCT01603407)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Adjusted group mean (CI)**	**Mean Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
TTRF velocity	Daily prednisone 0.75 mg/kg/day	65	0.236 (0.219 – 0.253)	0.06	0.03 to 0.08	0.003	N/A	N/A	N/A	The adjusted group mean for each corticosteroid regimen and the mean differences between the regimens were obtained from a repeated-measures analysis of covariance model with terms for treatment group, country, baseline weight-band dosage, the baseline value of the outcome variable, time (treated as a categorical variable), and interaction terms for the baseline value of the outcome variable × time and for treatment group × time [5].	[5]
	Intermittent prednisone 0.75 mg/kg/day (10 days on & 10 days off)	66	0.180 (0.163 – 0.197)								[5]

Results of FOR-DMD (NCT01603407)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Adjusted group mean (CI)**	**Mean Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
TTRF velocity	Daily deflazacort 0.90 mg/kg/day	65	0.240 (0.223 – 0.258)	0.06	0.03 to 0.09	0.17	N/A	N/A	N/A	The adjusted group mean for each corticosteroid regimen and the mean differences between the regimens were obtained from a repeated-measures analysis of covariance model with terms for treatment group, country, baseline weight-band dosage, the baseline value of the outcome variable, time (treated as a categorical variable), and interaction terms for the baseline value of the outcome variable × time and for treatment group × time [5].	(X)
	Intermittent prednisone 0.75 mg/kg/day (10 days on & 10 days off)	66	0.180 (0.163 – 0.197)								[5]
TTRF velocity	Daily prednisone 0.75 mg/kg/day	65	0.236 (0.219 – 0.253)	-0.004	-0.03 to 0.02	0.75	N/A	N/A	N/A	The adjusted group mean for each corticosteroid regimen and the mean differences between the regimens were obtained from a repeated-measures analysis of covariance model with terms for treatment group, country, baseline weight-band	[5]
	Daily deflazacort	65	0.240 (0.223 – 0.258)								[5]

Results of FOR-DMD (NCT01603407)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Adjusted group mean (CI)	Mean Difference	95% CI	*P* value	Difference	95% CI	*P* value		
	0.90 mg/kg/day									dosage, the baseline value of the outcome variable, time (treated as a categorical variable), and interaction terms for the baseline value of the outcome variable × time and for treatment group × time [5].	

Abbreviations: CI = Confidence interval; N/A = Not applicable.

Appendix C. Comparative analysis of efficacy

Table 60 Comparative analysis of studies comparing vamorolone to prednisone and deflazacort 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	LSM Difference (SE)	CI	P value	Difference	CI	P value		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	-[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[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	LSM Difference (SE)	CI	P value	Difference	CI	P value		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	-[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[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	LSM Difference (SE)	CI	P value	Difference	CI	P value		
[redacted]	[redacted]	-[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	-[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[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	LSM Difference (SE)	CI	P value	Difference	CI	P value		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]									

Table 61. Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety (VISION-DMD and matched subjects in FOR-DMD)

Variable	VISION-DMD		FOR-DMD
	Vamorolone 6.0 mg/kg/day	Prednisone 0.75 mg/kg/day	Deflazacort 0.90 mg/kg/day
Age			
n	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]

Min, Max	[redacted]	[redacted]	[redacted]
Region			
Europe	[redacted]	[redacted]	[redacted]
USA	[redacted]	[redacted]	[redacted]
Height (cm)			
n	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]
Height Percentile			
n	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]
Height z-score			
n	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]

Weight (kg)			
n	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]
Weight Percentile			
n	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]
Weight z-score			
n	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]
BMI (kg/m^2)			
n	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]

Median	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]
BMI Percentile			
n	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]
BMI z-score			
n	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]

Abbreviations: BMI = body mass index; cm = centimetre; kg = kilogram; max = maximum; min = minimum; m^2 = square metre; mg = milligram; n = number; SD = standard deviation. Source: [78]

Table 62 Assessment of Impact on Functioning DMD at Baseline for External Comparison of Study VISION-DMD and Matched Subjects in the FOR-DMD

Outcome	VISION-DMD	FOR-DMD	
	Vamorolone 6.0 mg/kg/day (n = 27)	Prednisone 0.75 mg/kg/day (n = 39)	Deflazacort 0.90 mg/kg/day (n = 47)
TTSTAND Velocity (rises/sec)	[redacted]	[redacted]	
Mean	[redacted]	[redacted]	[redacted]
SD			

Median	Xxxxx	Xxxxx	Xxxxx
Min, Max	Xxxxx	Xxxxx	Xxxxx
TTSTAND Velocity (rises/sec)	Xxxxx	Xxxxx	Xxxxx
Mean	Xxxxxx	Xxxxxx	xxxxxxx

Abbreviations: kg = kilogram; Max = maximum; Min = minimum; mg = milligram; n = number; sec = second; SD = standard deviation; TTSTAND = Time to Stand. Source: [78]

Table 63 Baseline in matched prednisone groups in VISION-DMD and FOR-DMD

Outcome	VISION-DMD	FOR-DMD
	Prednisone 0.75 mg/kg/day (N = 31)	**Prednisone 0.75 mg/kg/day (N = 37)**
TTSTAND velocity (rises/sec)		
Mean	Xxxxxxx	xxxxxxx
SD	Xxxxx	Xxxxx
Median	Xxxxx	Xxxxx
Min, Max	Xxxxxx	xxxxxx

Abbreviations: kg = kilogram; Max = maximum; Min = minimum; mg = milligram; N = number; sec = second; SD = standard deviation; TTSTAND, Time to Stand. Source: [78]

Table 64 Height absolute Values, percentiles and z-scores at baseline and change at Month 6 for and Matched Prednisone Groups in VISION-DMD and FOR-DMD

Outcome	VISION-DMD	FOR-DMD

	Prednisone 0.75 mg/kg/day (N = 31)	Prednisone 0.75 mg/kg/day (N = 37)
Height (cm)		
Baseline		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Change at Month 6		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Percentile		
Baseline		

Mean (SD)	Xxxx	Xxxx
Median	Xxxxxx	Xxxxxxx
Min, Max	Xxxx	Xxxx
Change at Month 6	Xxxxx	Xxxx
n		
Mean (SD)	Xx	Xx
Median	Xxxxxx	Xxxxxxxxx
Min, Max	Xxxxx	Xxxxx
z-score	Xxxxxxxxx	xxxxxx
Baseline		
n		
Mean (SD)	Xxx	Xx
Median	Xxxxxx	Xxxxxx
Min, Max	Xx	Xxx

Change at Month 6	[redacted]	[redacted]
n		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Change at Month 6	[redacted]	[redacted]

Abbreviations: mg = milligram; kg = kilogram; Max = maximum; Min = minimum; mg = milligram; N = number; SD = standard deviation; cm = centimetre. Source: [78]

Table 65 Overview of TEAEs in Matched Prednisone Groups in VISION-DMD and FOR-DMD

Variable	Matched Population	
	VISION-DMD	FOR-DMD
Type of AEs	Prednisone 0.75 mg/kg/day (N = 31) n (%); f (Rate)	Prednisone 0.75 mg/kg/day (N=50) n (%); f (Rate)
Total number of TEAEs	[redacted]	[redacted]
Any Drug related TEAEs	[redacted]	[redacted]
Clinically relevant TEAEs	[redacted]	[redacted]
Serious TEAEs	[redacted]	[redacted]
TEAEs of special interest	[redacted]	[redacted]
TEAEs leading to permanent study treatment discontinuation	[redacted]	[redacted]

Note: For FOR-DMD the population is patients receiving daily Prednisone or Deflazacort and who fulfilled similar inclusion criteria to the VISIOND-DMD patients. Inclusion criteria for FOR-DMD: Confirmed DMD, age between 4 and 7 at informed consent, pre-treatment Time to Stand time (without assistance) and Six-minute Walk Test distance are available in the data. TEAEs with onset before the subject's Week 24 (VISIOND-DMD) or Month 06 (FOR-DMD) Visit are included. Note: Clinically Relevant AEs are either at least moderate in severity or leading to withdrawal from study or serious event. Rate is calculated as Events per patient per year of exposure.
Abbreviations: AE = adverse event; f = event count; n = Number of subjects; TEAE = treatment-emergent adverse event; mg = milligram; kg = kilogram.

Table 66 Frequency of TEAEs by Severity in Matched Prednisone Groups in VISION-DMD and FOR-DMD

	Matched Population	
	VISION-DMD	FOR-DMD
Severity of AEs	Prednisone 0.75 mg/kg/day (F=102) f (%)	Prednisone 0.75 mg/kg/day (F=160) f (%)
Mild	[redacted]	[redacted]
Moderate	[redacted]	[redacted]
Severe	[redacted]	[redacted]

Note: For VISION-DMD study the population is patients receiving prednisone during Period 1. For FOR-DMD the population is patients receiving daily Prednisone and who fulfilled similar inclusion criteria to the VISION-DMD patients. Rate is calculated as number of AEs per patient-year. For FOR-DMD exposure and AEs are limited to 6 Months Visit Date. Abbreviations: AE = adverse event; f = event count; n = Number of subjects; mg = milligram; kg = kilogram.

Appendix D. Extrapolation

Extrapolation of [effect measure 1]

All information about extrapolation of effect measures is included in section 8.1.

Data input

Model

Proportional hazards

Evaluation of statistical fit (AIC and BIC)

Evaluation of visual fit

Evaluation of hazard functions

Validation and discussion of extrapolated curves

Adjustment of background mortality

Adjustment for treatment switching/cross-over

Waning effect

Cure-point

Extrapolation of [effect measure 2]

Appendix E. Serious adverse events

Serious adverse events (SAE) were defined as any AE regardless of causality that met any of the following criteria:

- resulted in death
- was life-threatening
- required inpatient hospitalization or prolongation of an existing hospitalization
- resulted in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- resulted in a congenital anomaly/birth defect
- was an important medical event that may have jeopardized the subject and may have required medical or surgical intervention to prevent one of the outcomes listed above.

Hospitalizations for <24 hours or emergency room visits were not considered SAEs. Additionally, scheduled hospital admissions were not considered SAEs, unless the hospitalization was prolonged due to an AE.

No deaths, SAEs, or AEs leading to permanent discontinuation of study drug were reported following the switch from prednisone in Period 1 to vamorolone in Period 2.

Table 67 Serious adverse events reported in VISION-DMD

SAEs reported during both study periods of VISION-DMD			
Study period 1 – Safety population 1			
Study arms	**Vamorolone 6.0mg (N=28)**	**Placebo (N=29)**	**Prednisone 0.75mg (N=31)**
Total Serious TEAEs	0	0	0
Study period 2 – Safety population 2			
	Vamorolone 6.0mg (N=28) f(Rate); n(%)	**Prednisone 0.75mg + Vamorolone 6.0mg (N=15) f(Rate); n(%)**	**Placebo + Vamorolone 6.0mg (N=14) f(Rate); n(%)**
Total Serious TEAEs	2 (0.077); 2 (7.1%)	0	0
Infections and infestations (Appendicitis perforated)	1 (0.039); 1 (3.6%)	0	0
Respiratory, thoracic and mediastinal disorders (Asthma)	1 (0.039); 1 (3.6%)	0	0

Note: Treatment-emergent adverse events (TEAEs) are defined as any adverse event starting or worsening after initiation of the investigational product and through the subject's last study visit (study completion or early termination). Serious adverse events (SAEs) were recorded for up to 30 days after the final administration of study drug. For the Period 1 analyses, AEs, SAEs and TEAEs with onset through the subject's Week 24 F/U Visit are included. Period 2 includes transition phase for subjects who had Vamorolone on both Periods. Tapering phase is included in Period 2 for subjects who didn't continue to early access programme.

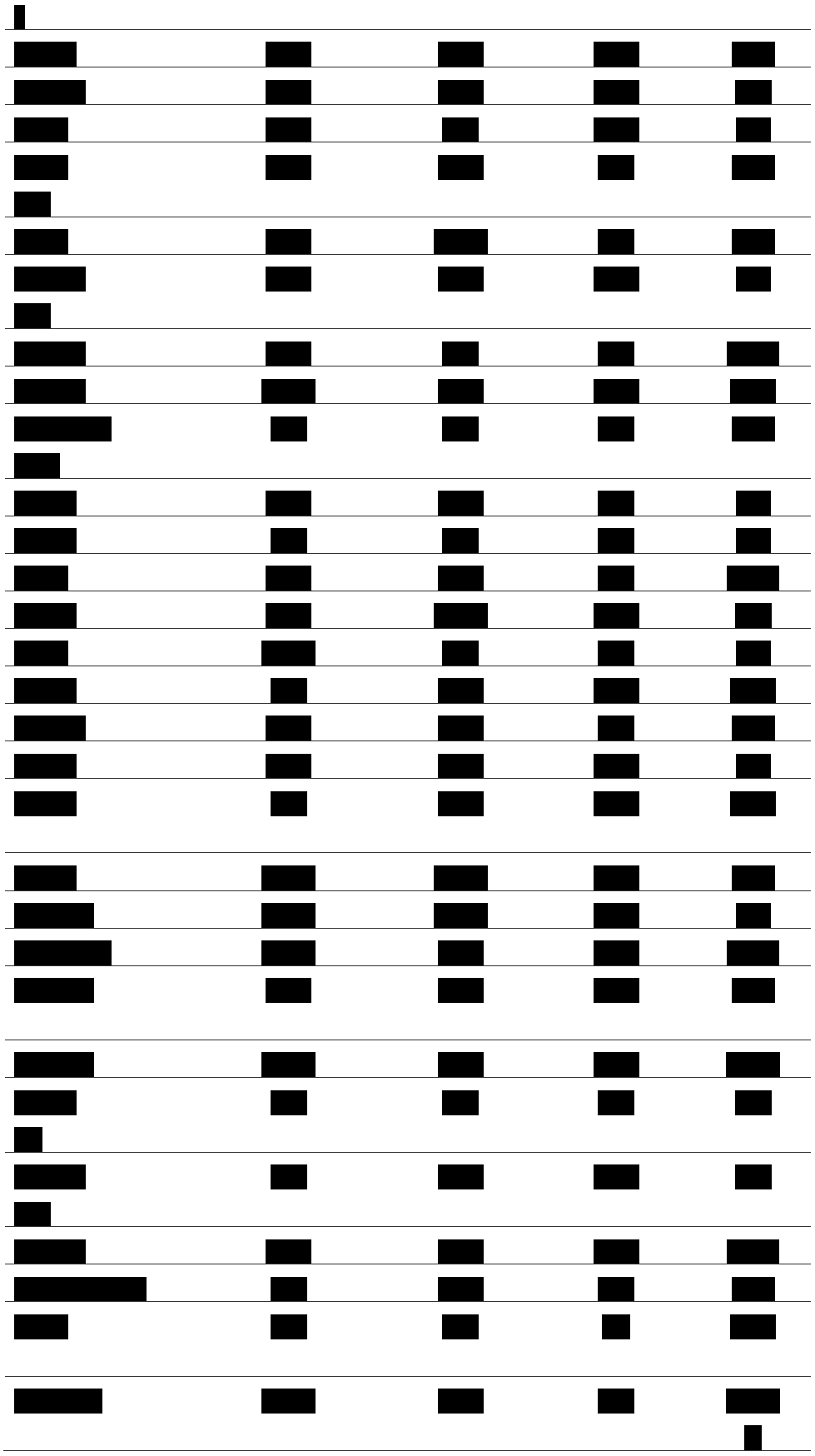
Appendix F. Health-related quality of life

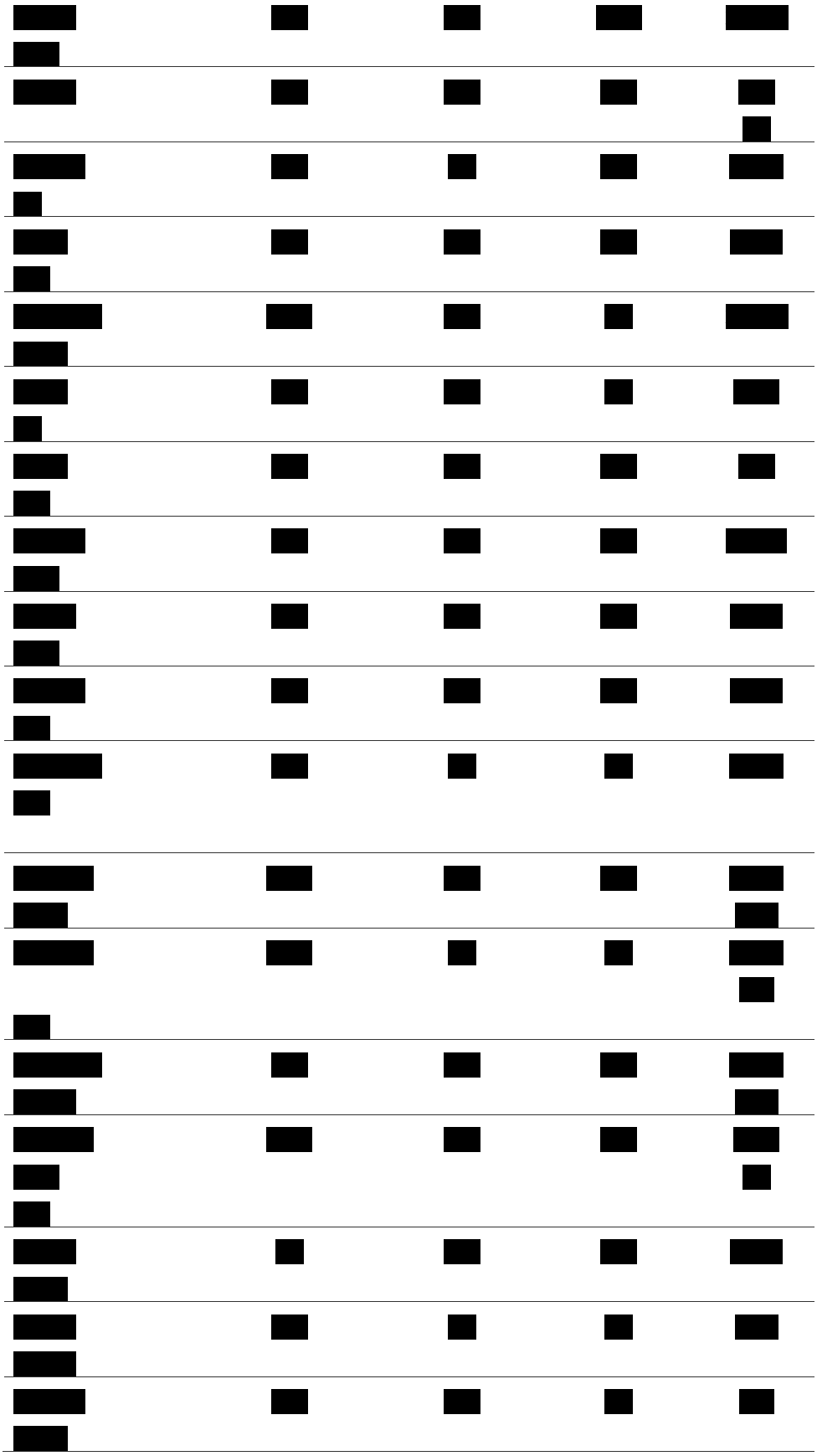
Not applicable.

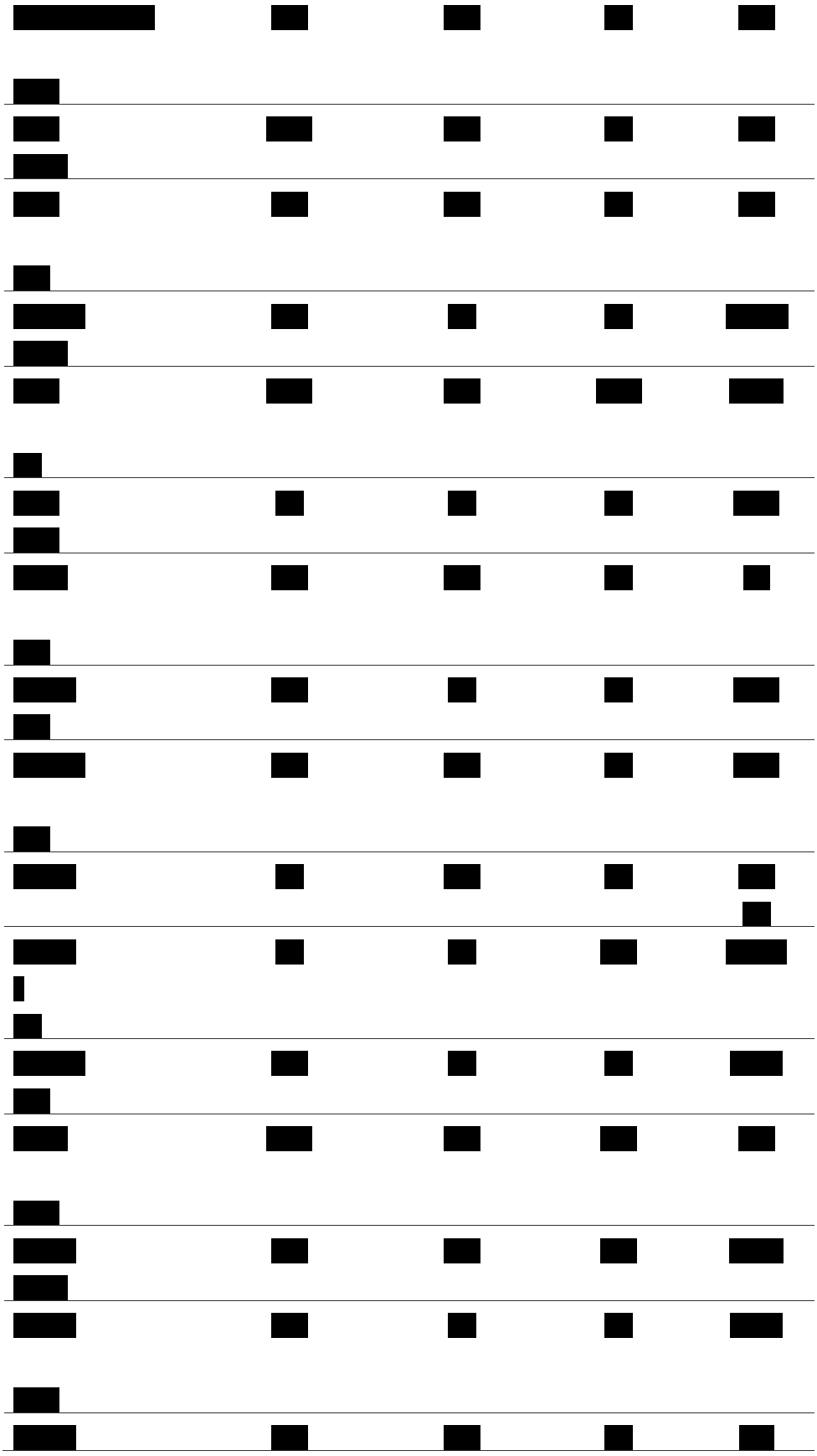
Appendix G. Probabilistic sensitivity analyses

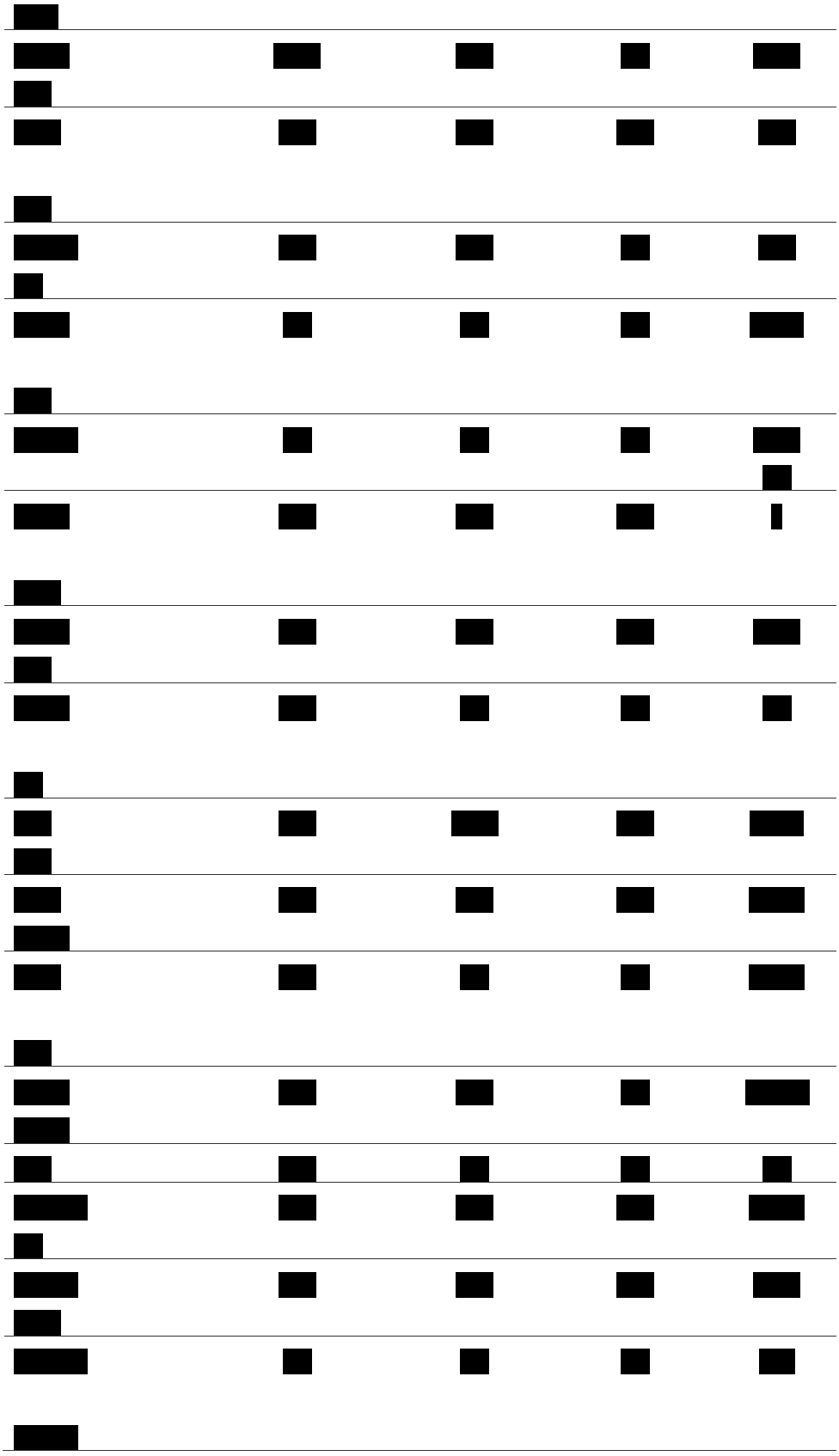
Table 68 Overview of parameters in the PSA

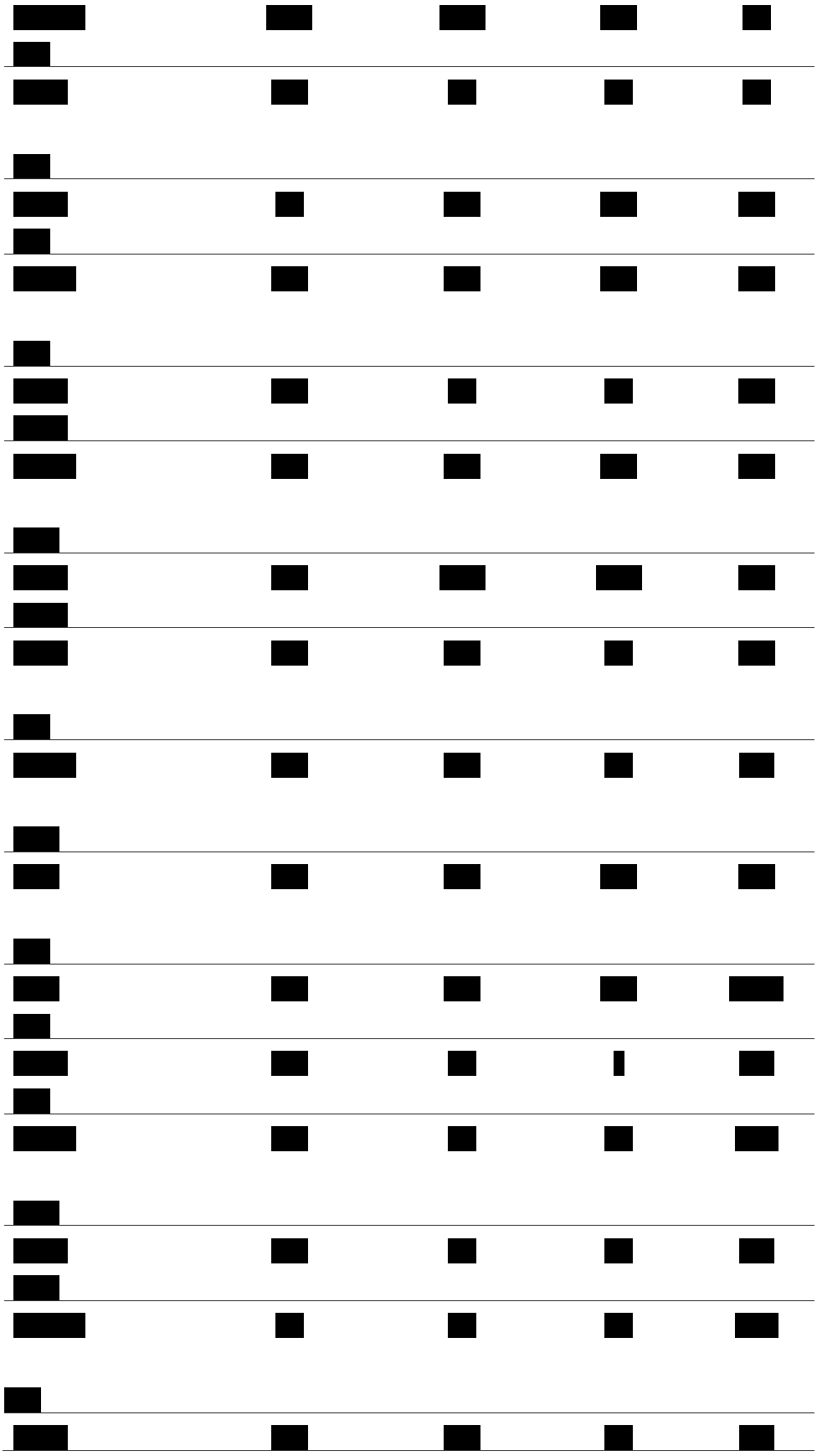
Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
[redacted]				

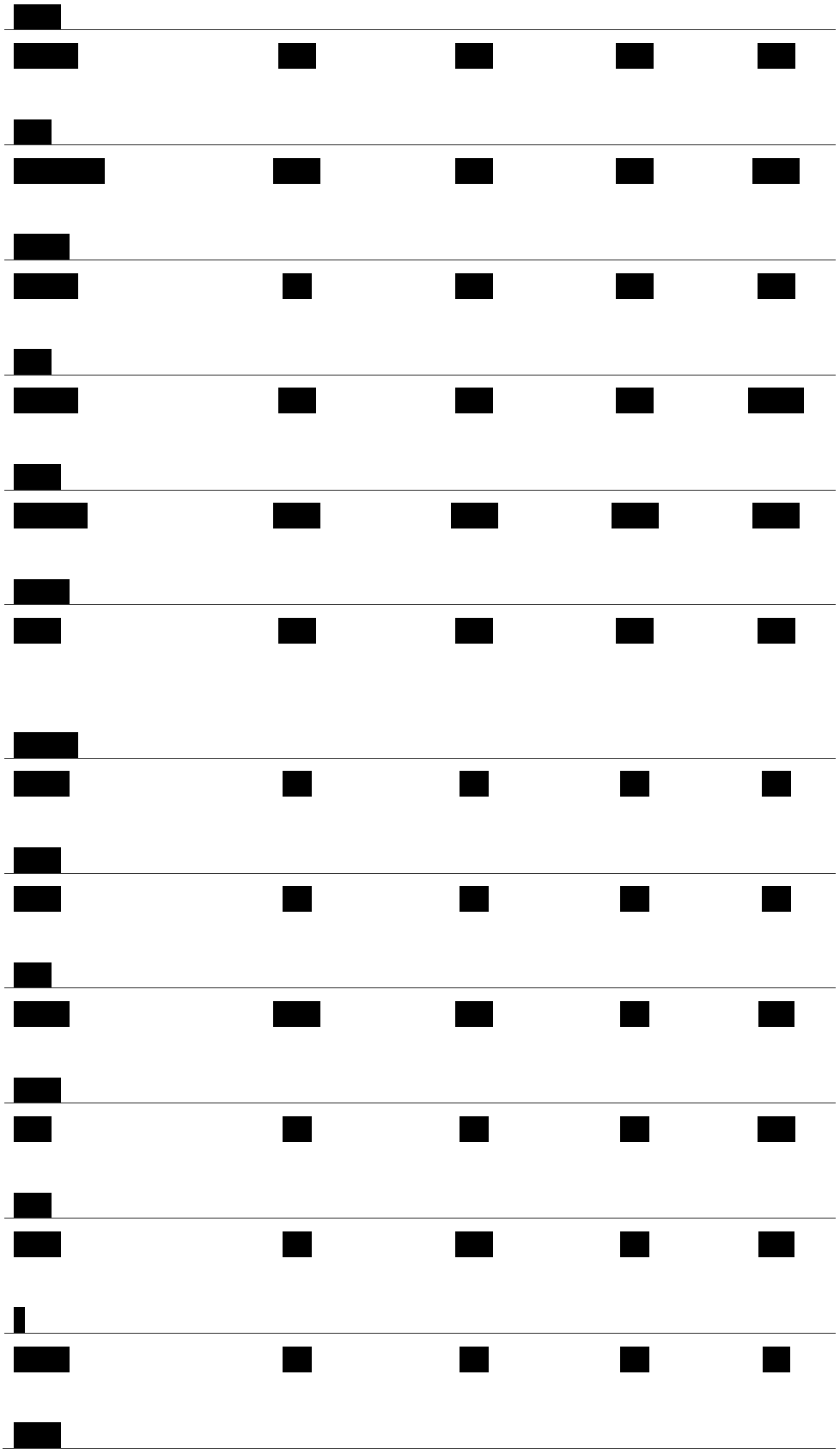


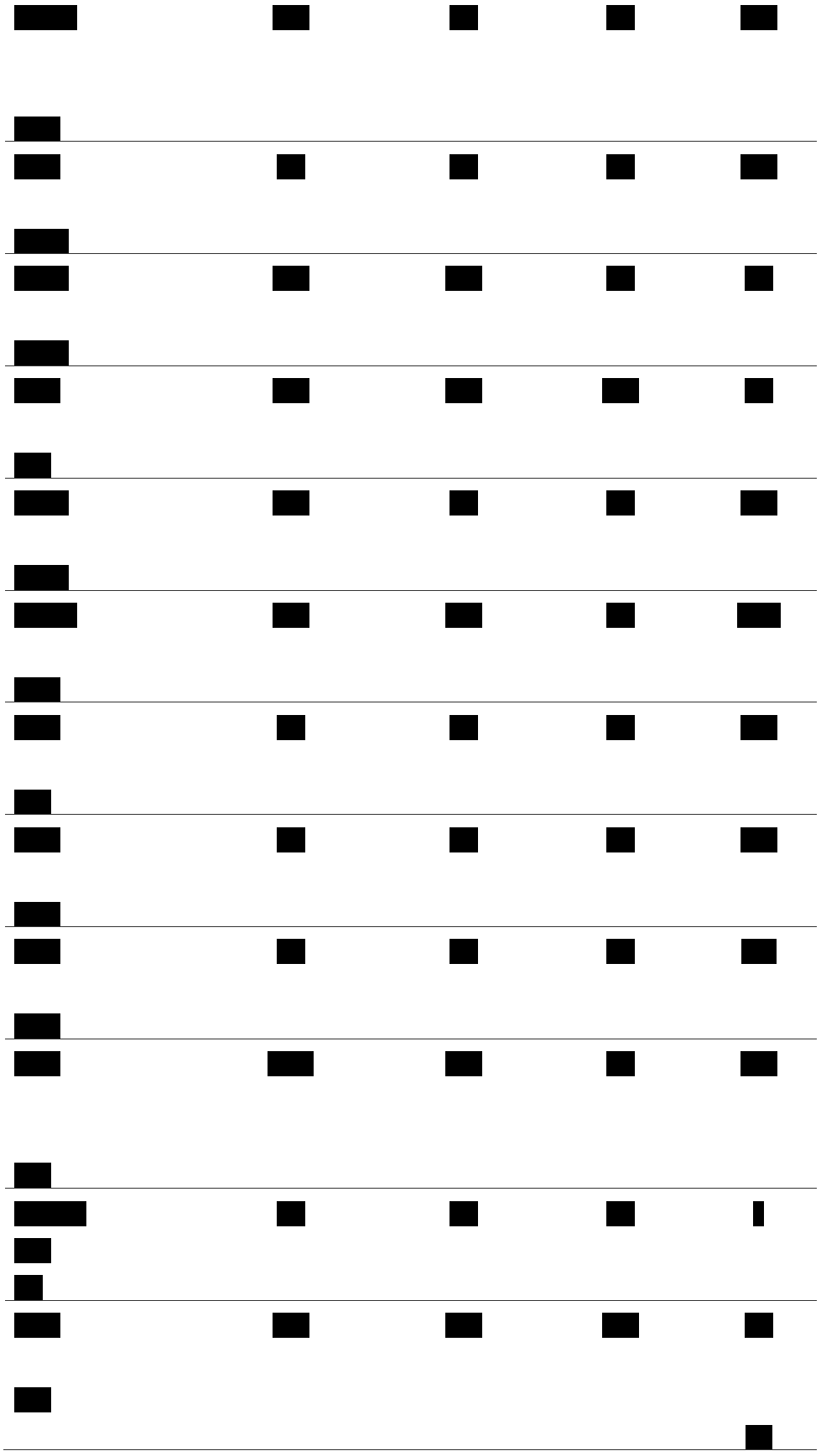


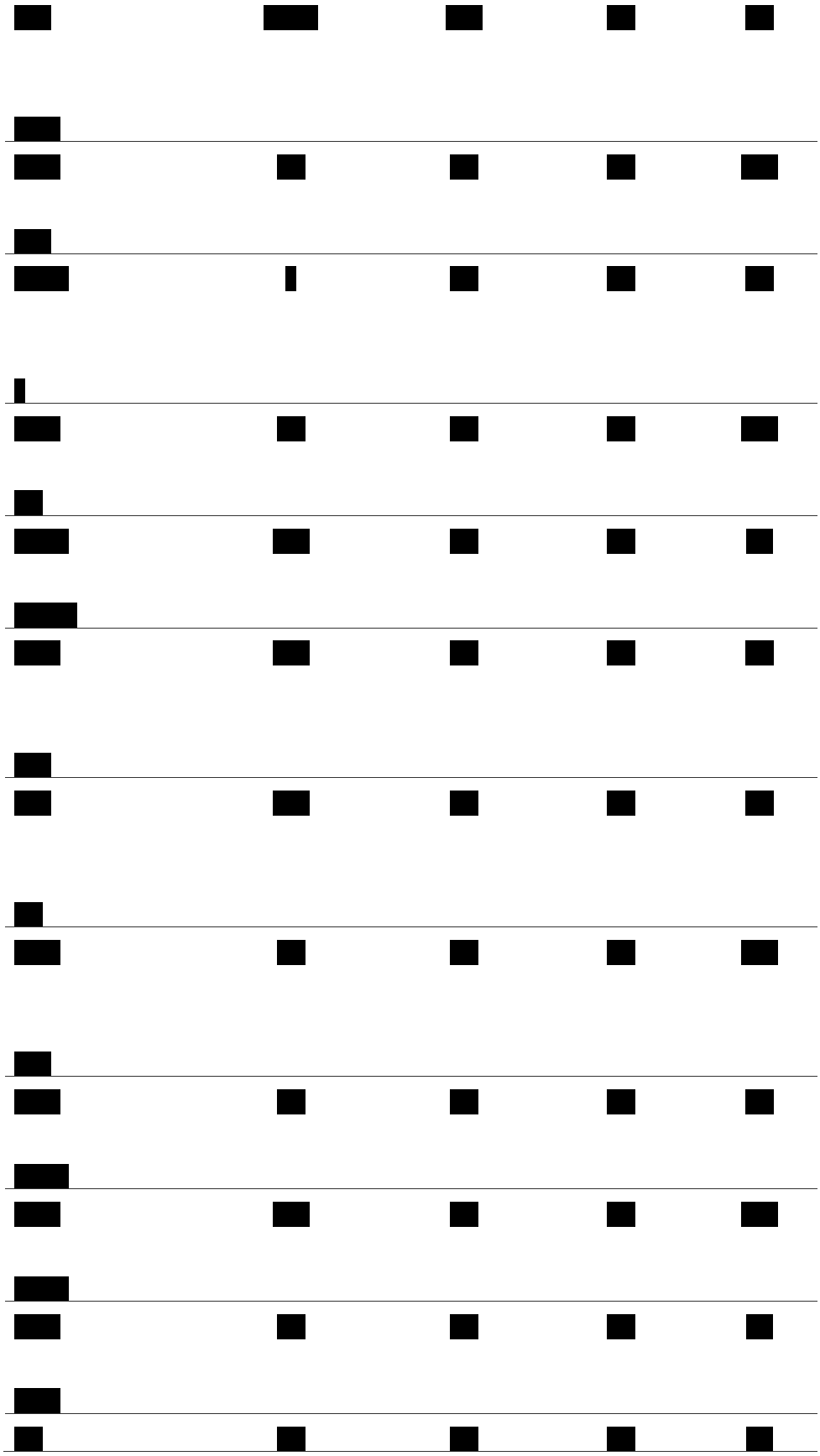


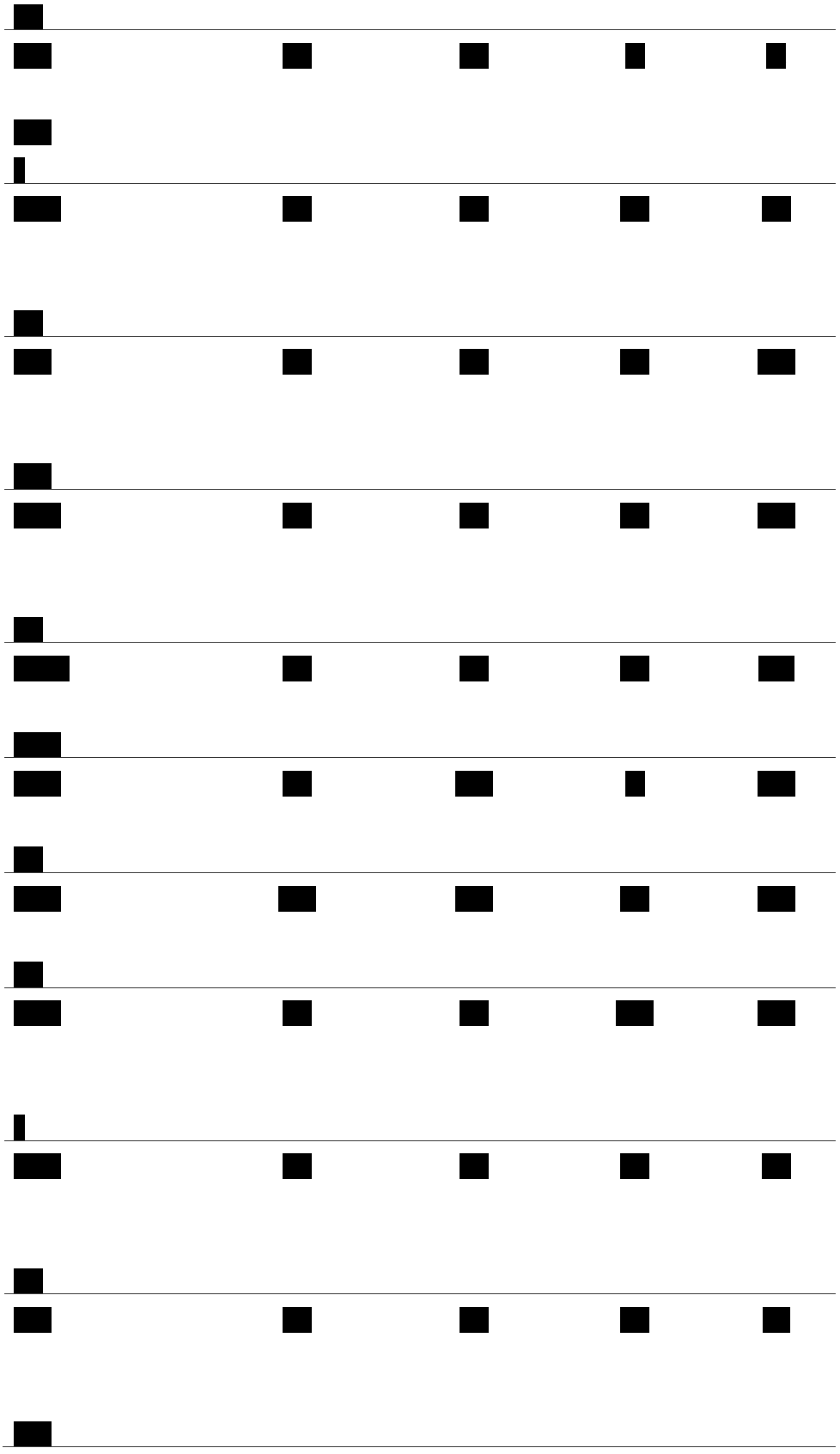


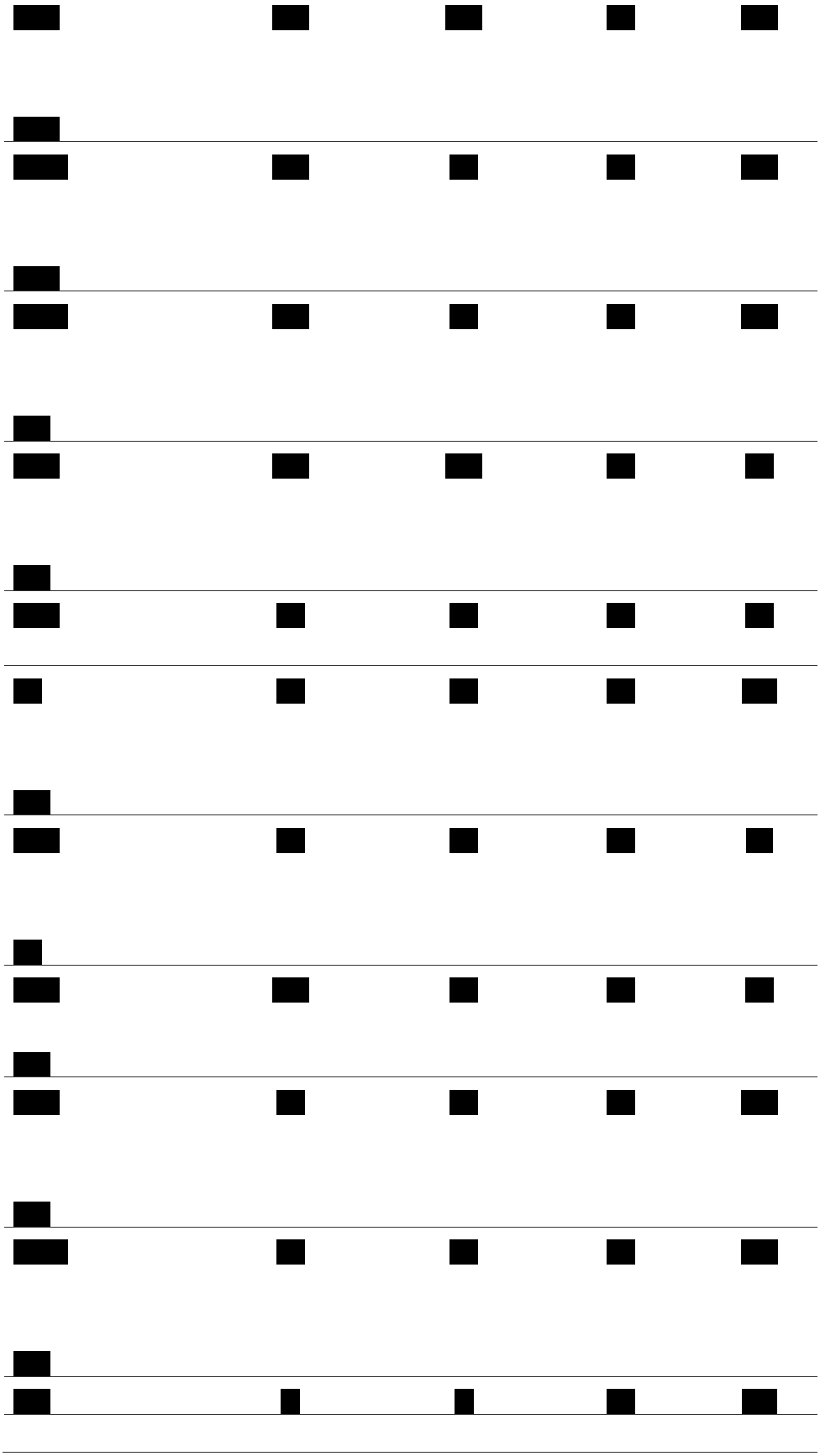


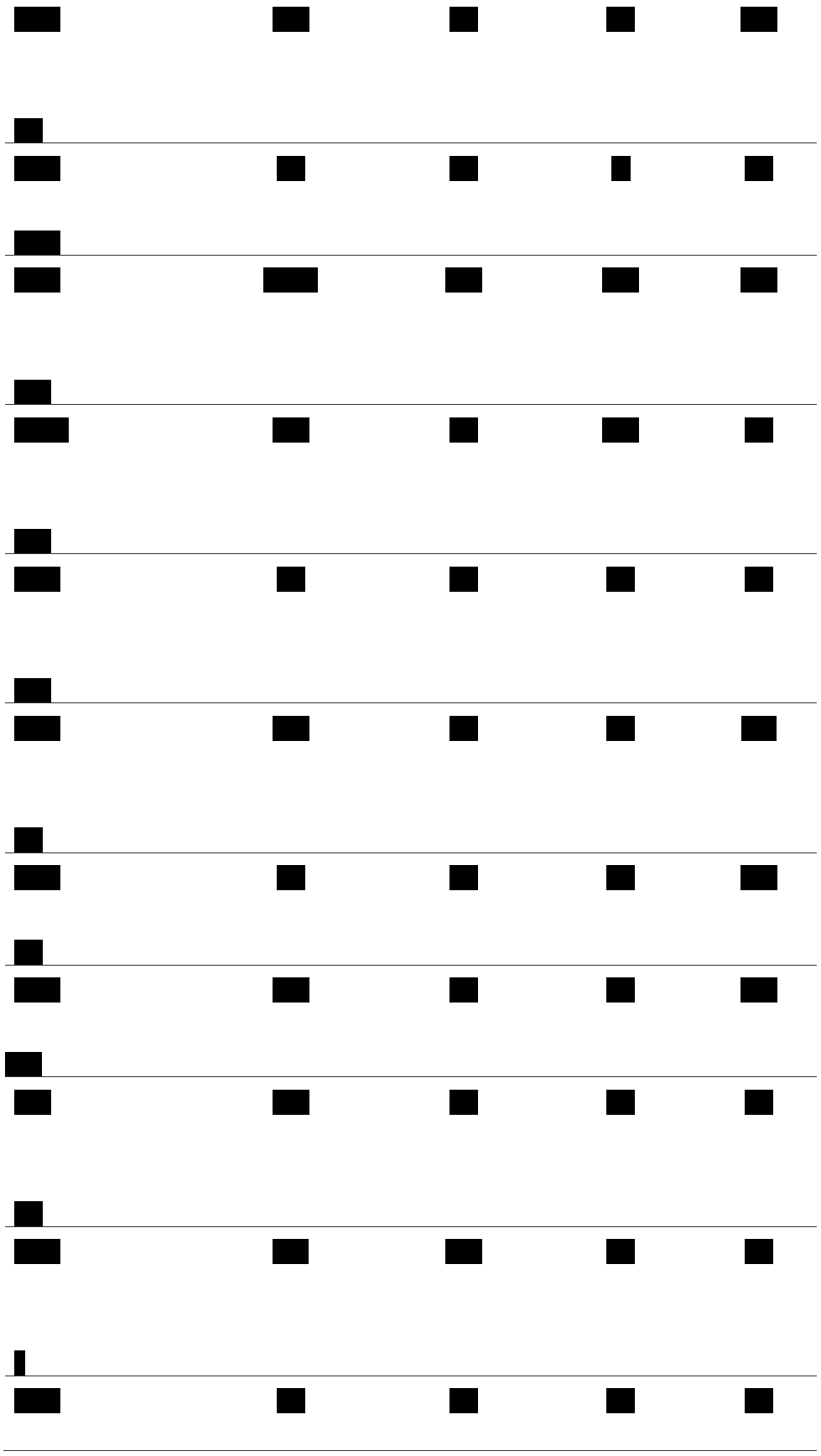


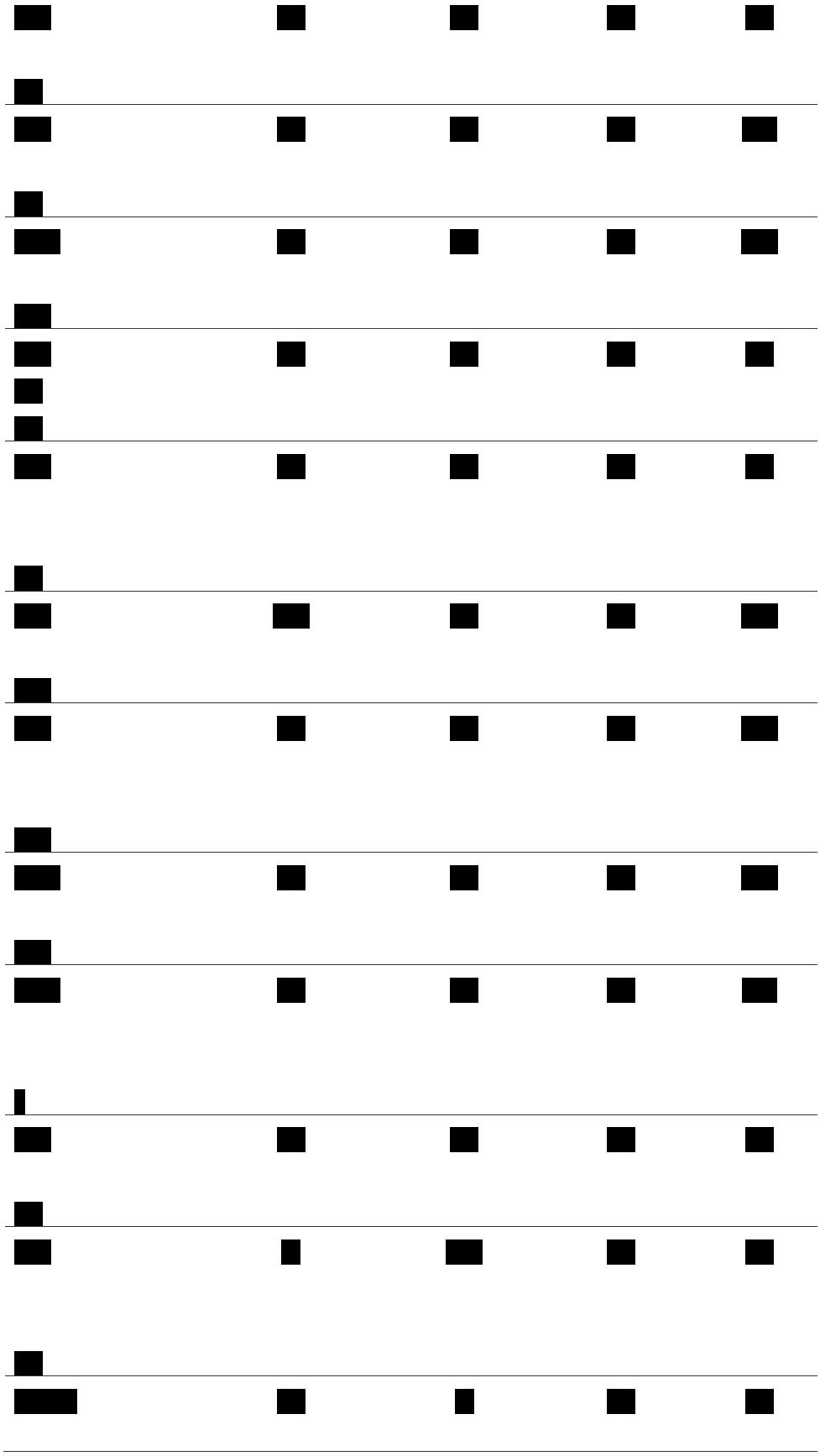


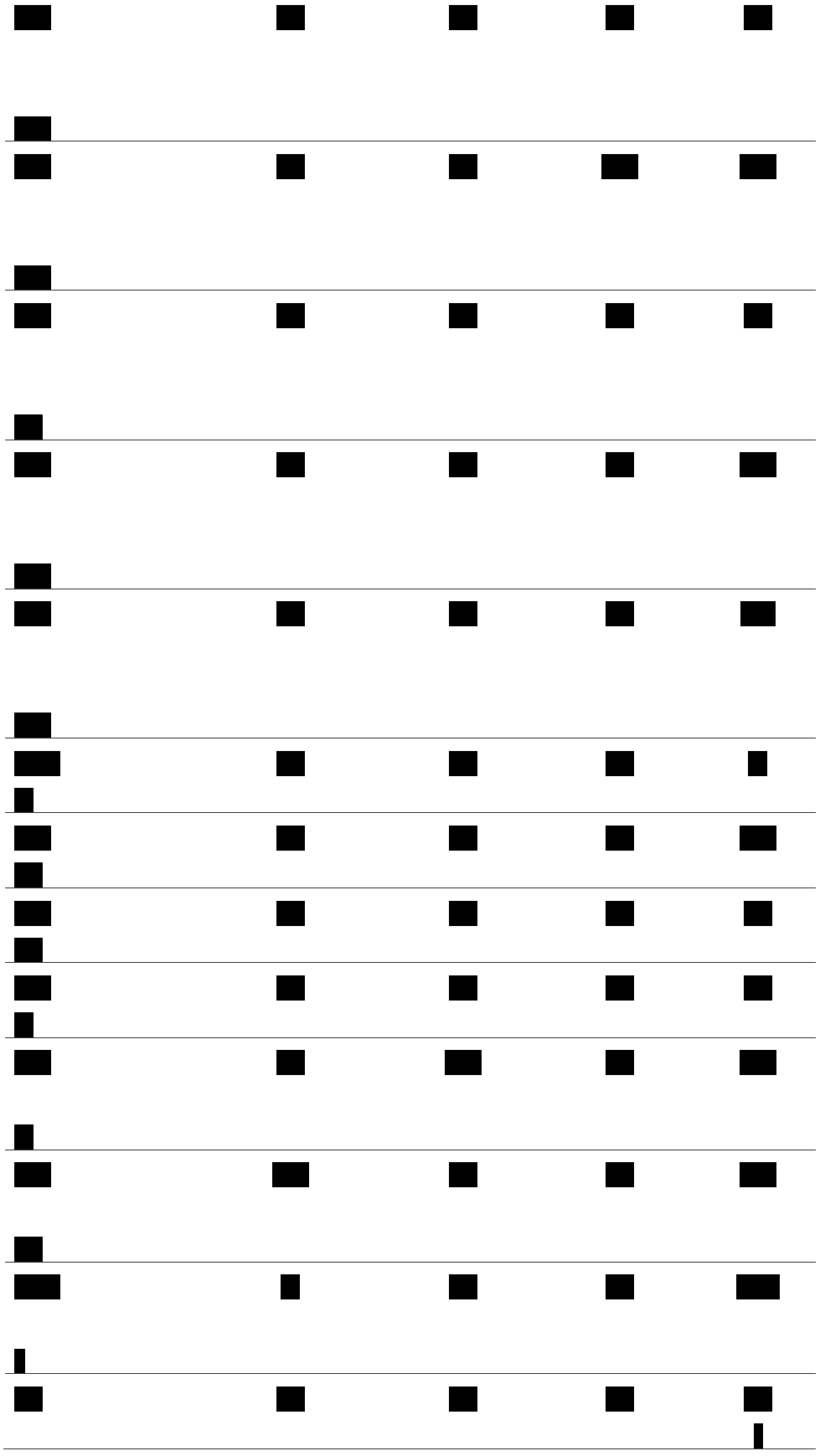


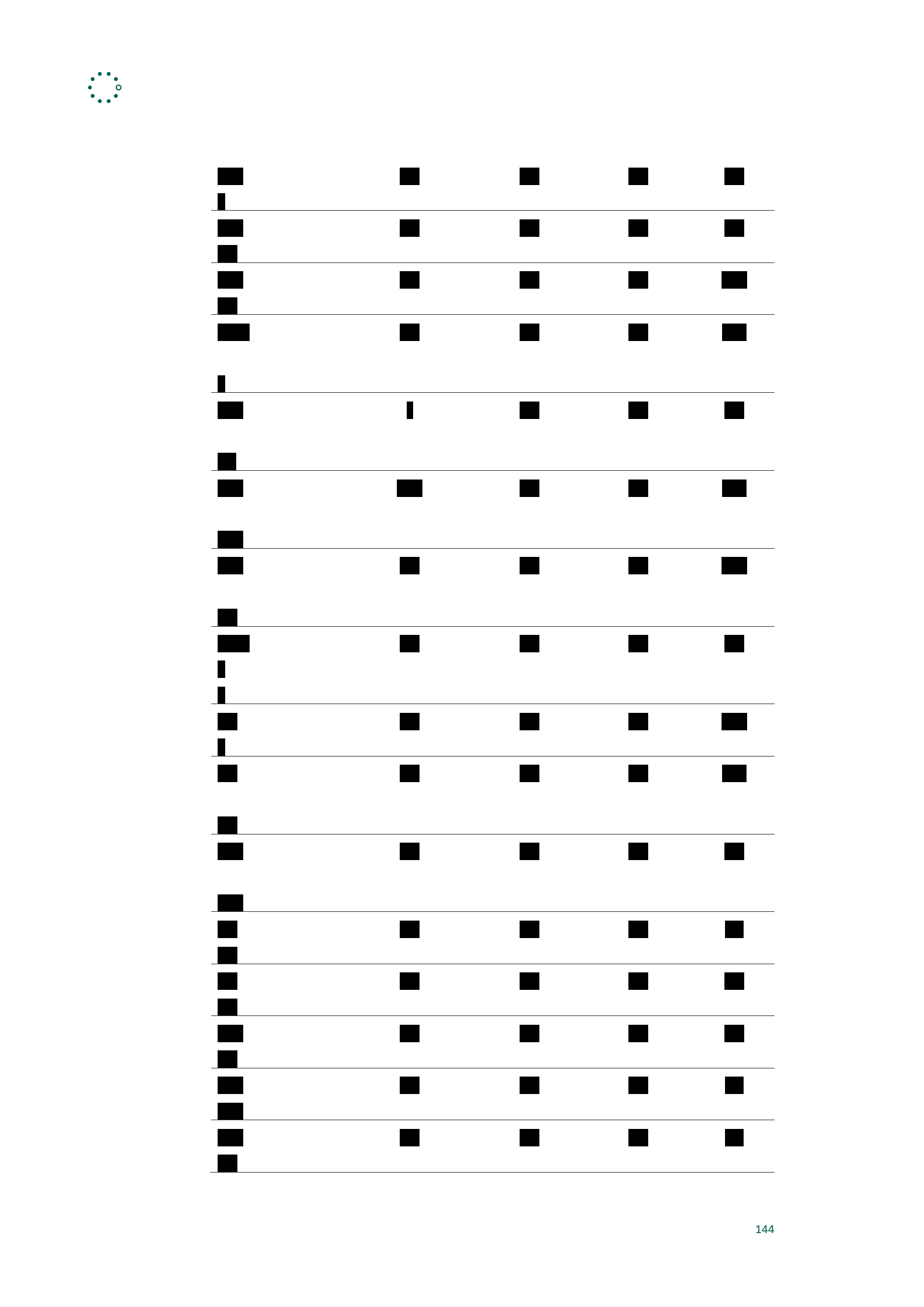


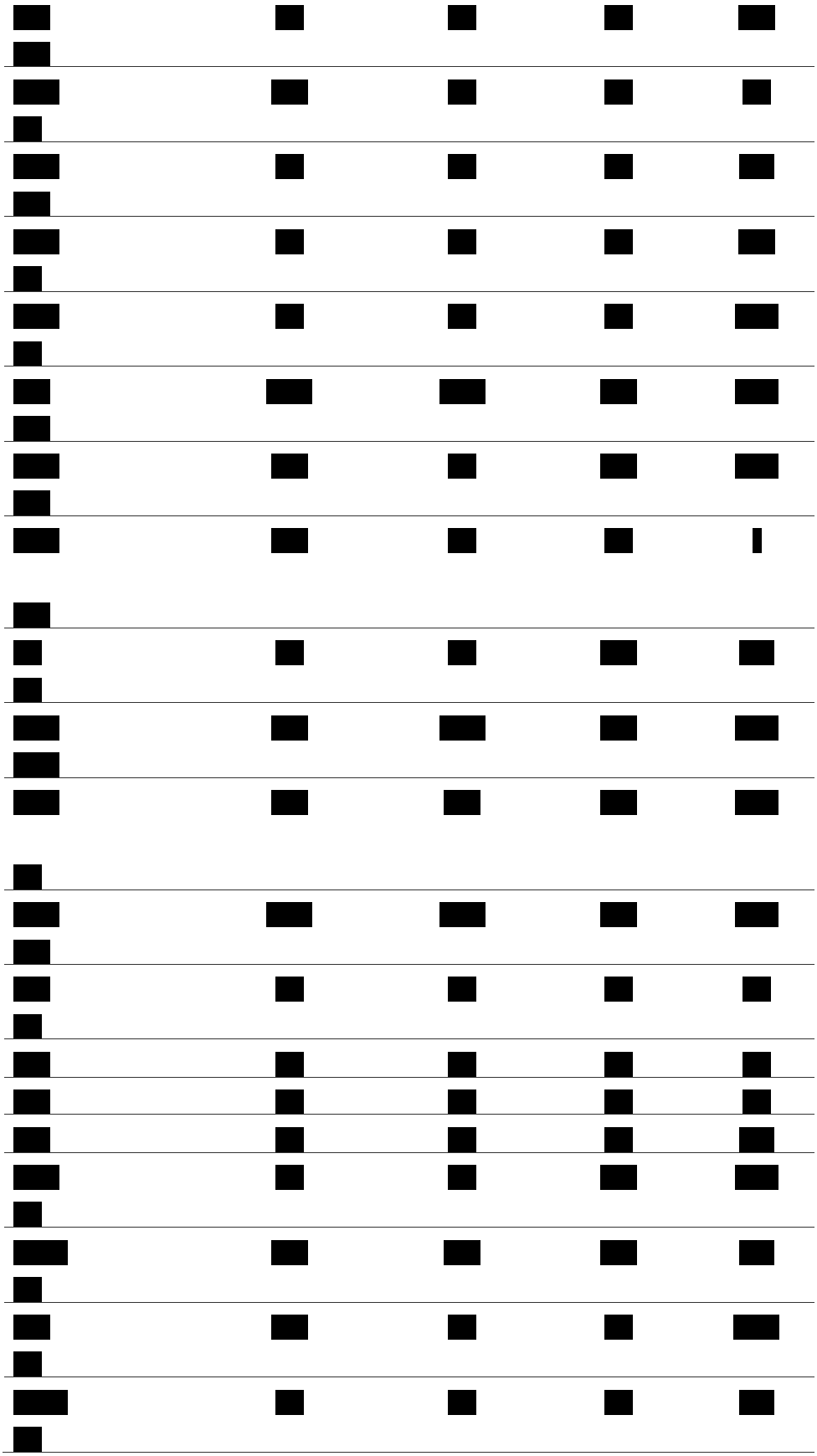


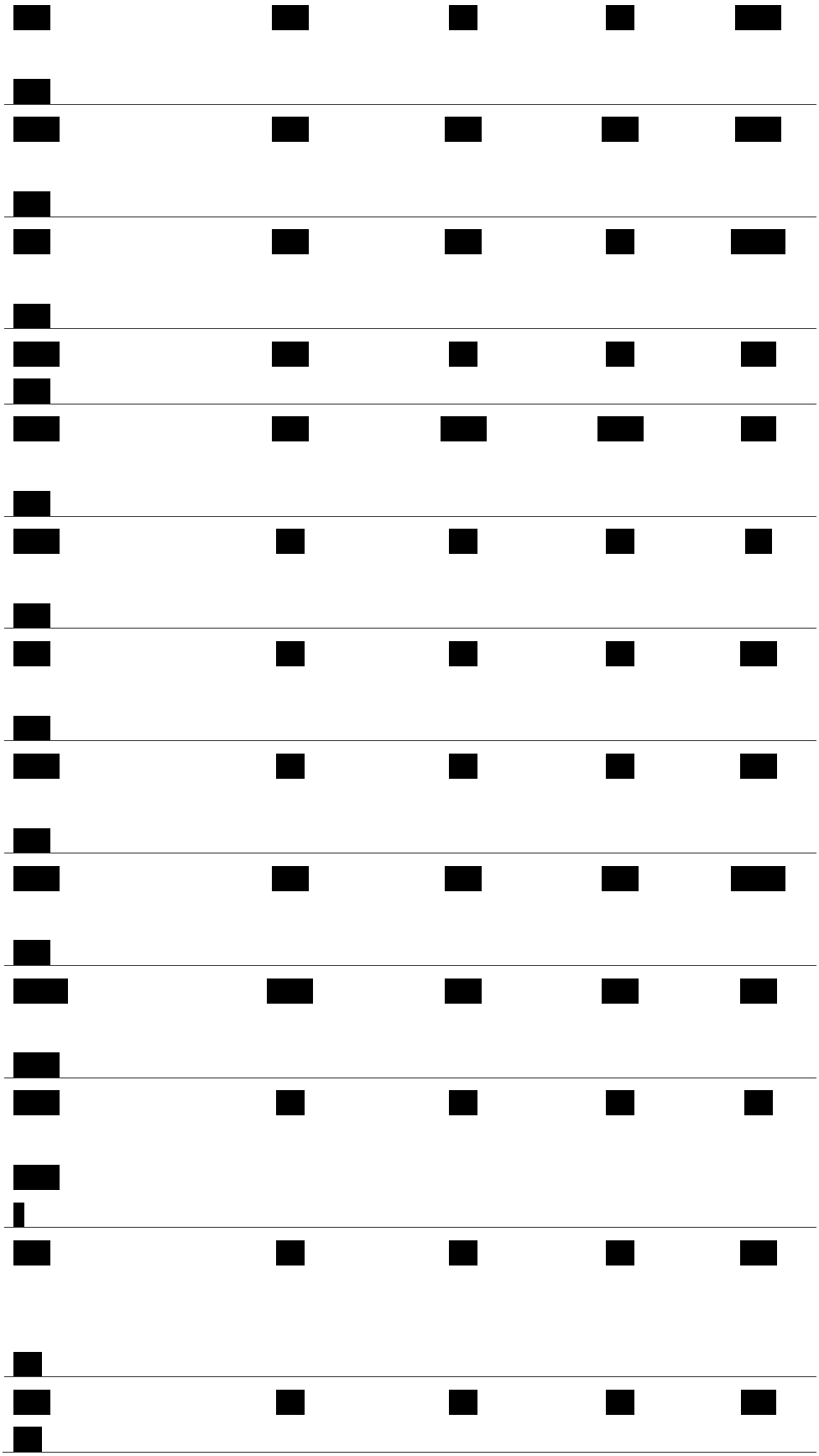


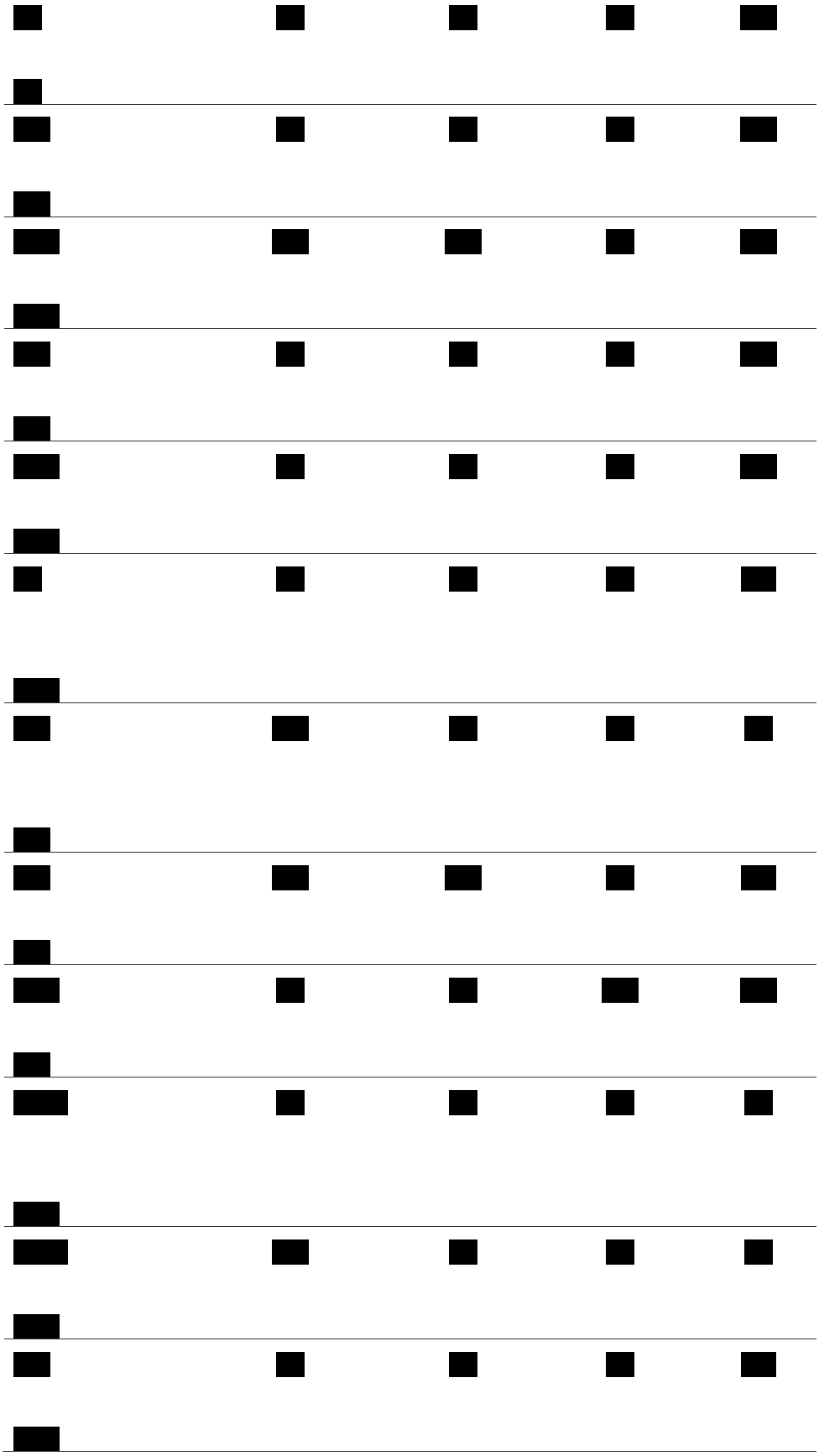


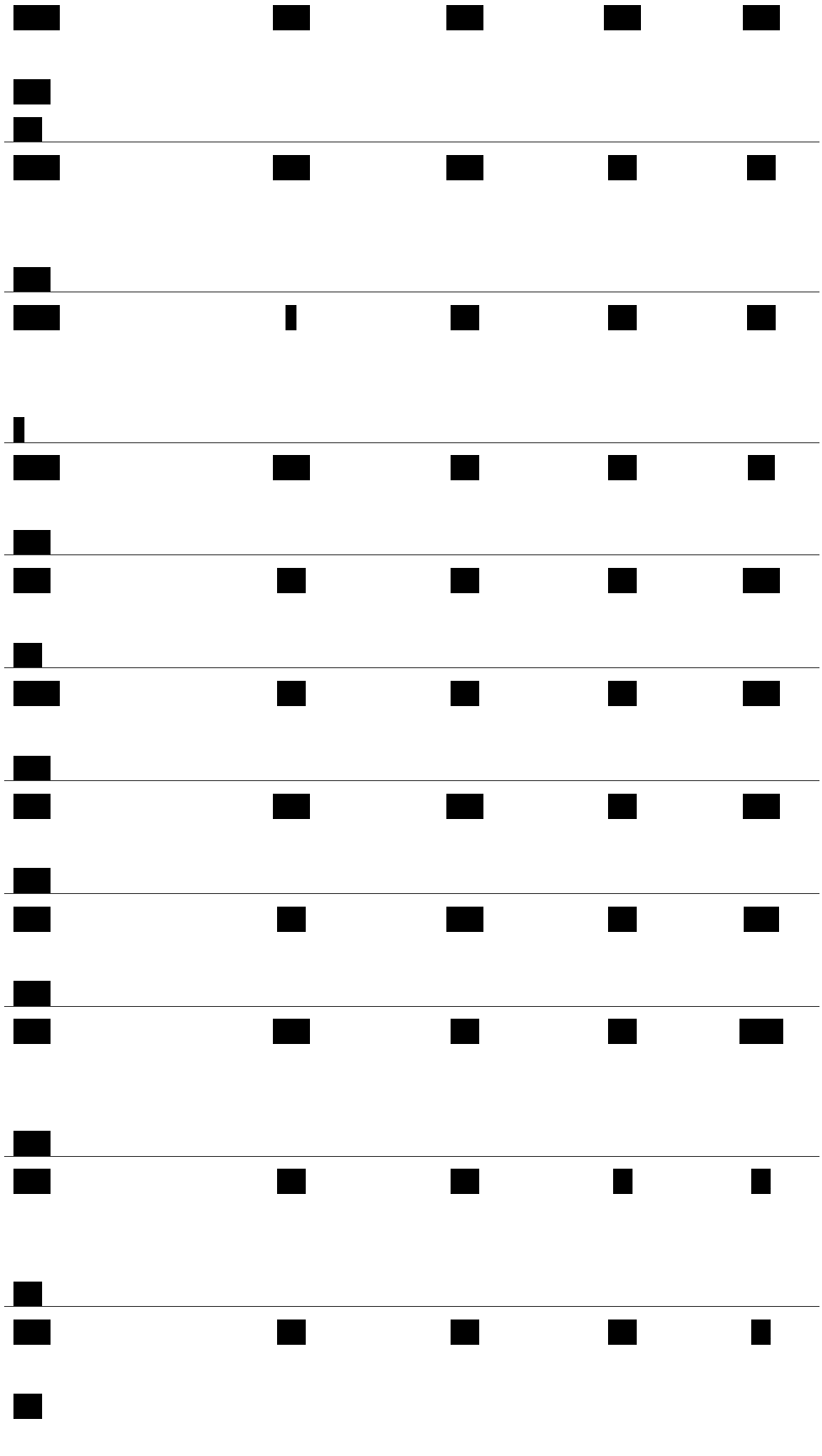


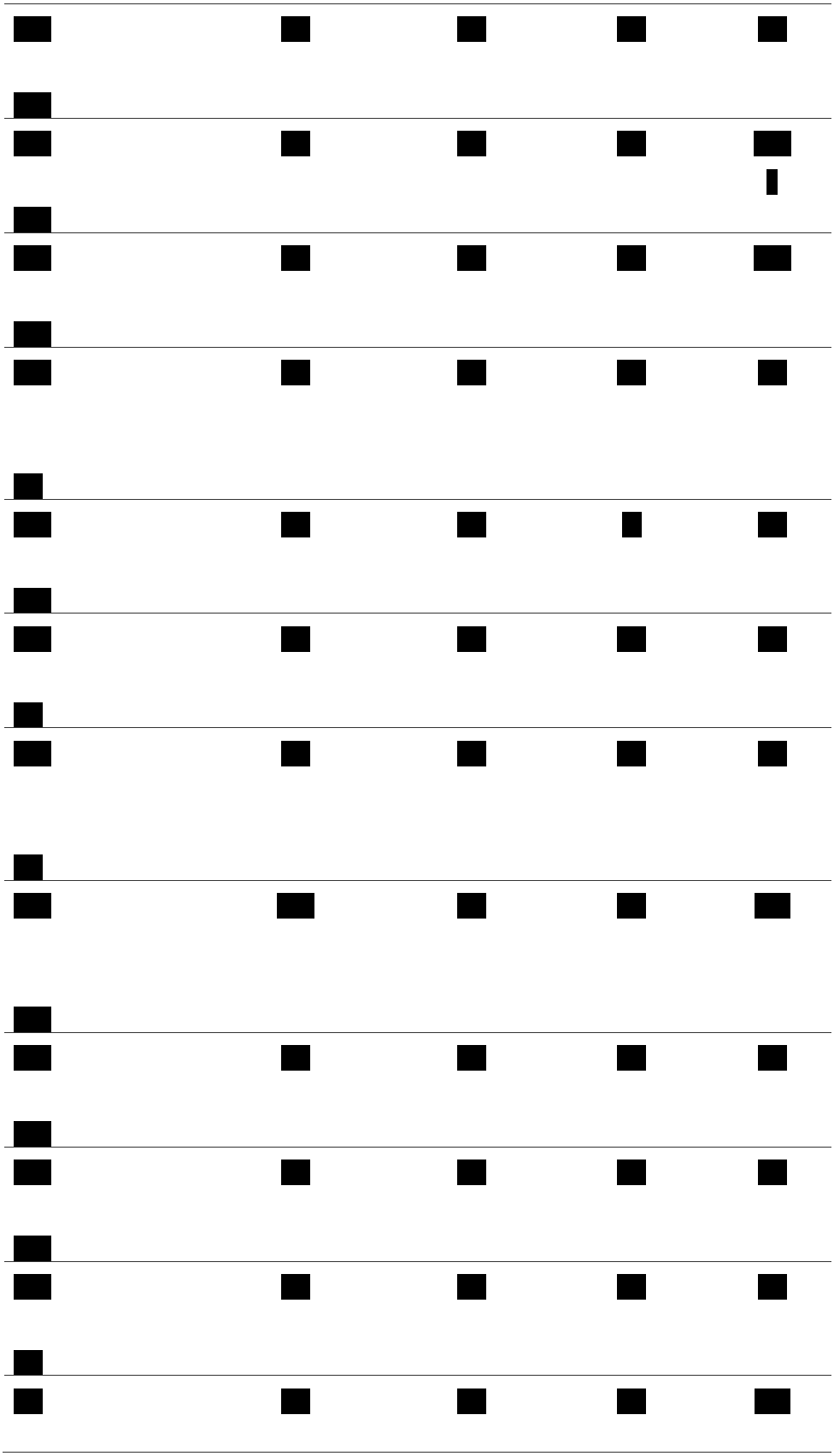


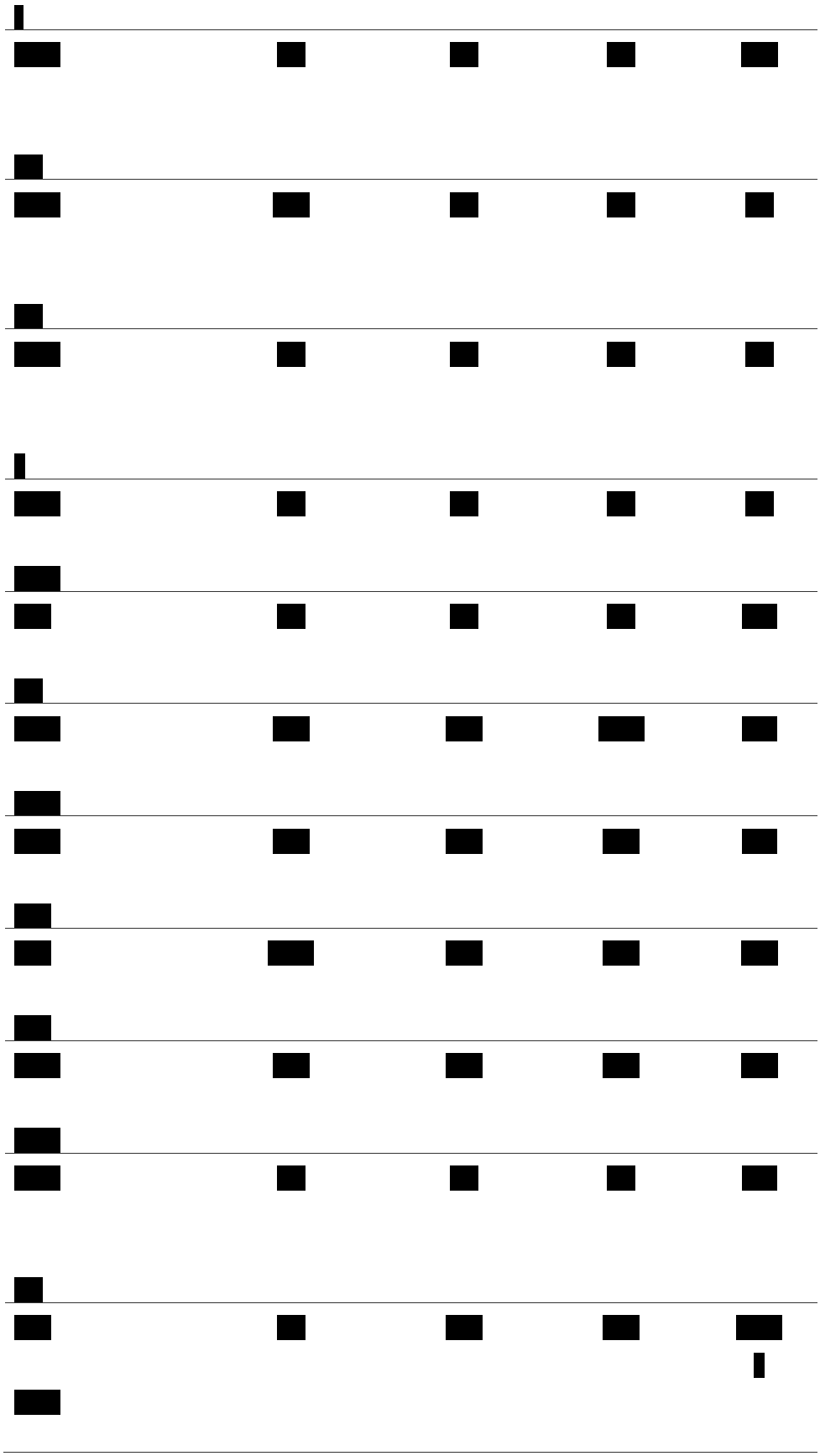


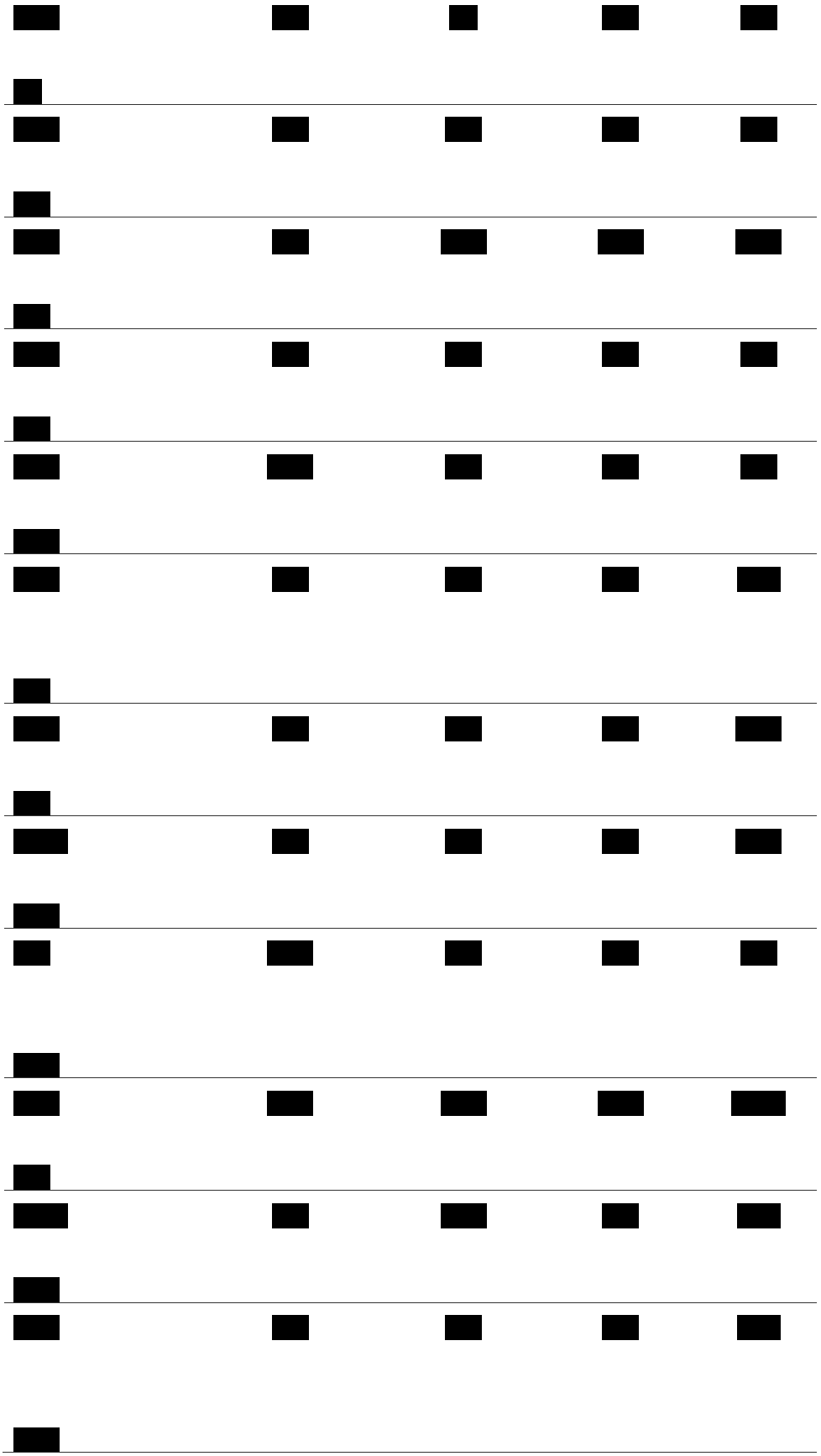


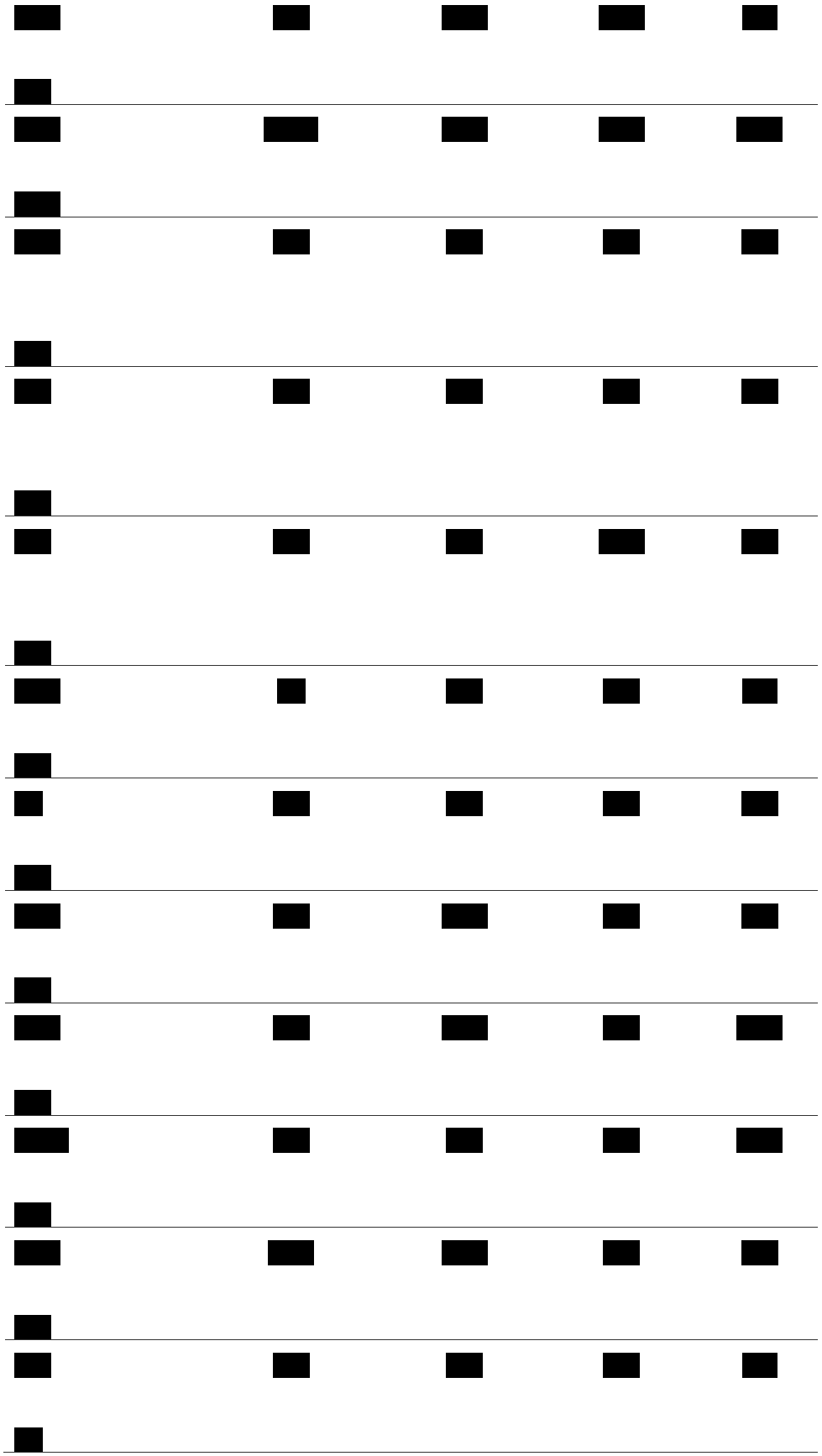


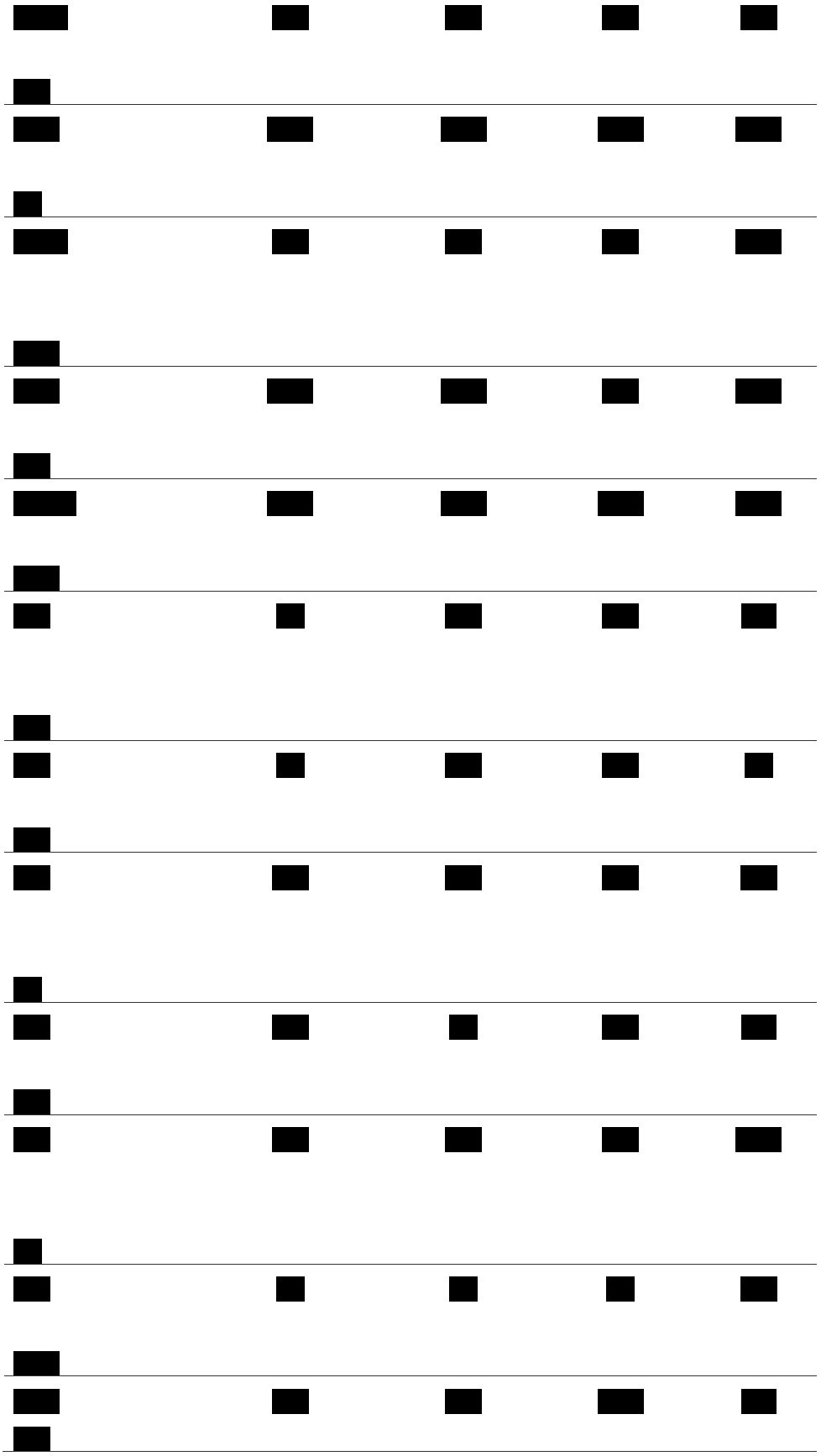


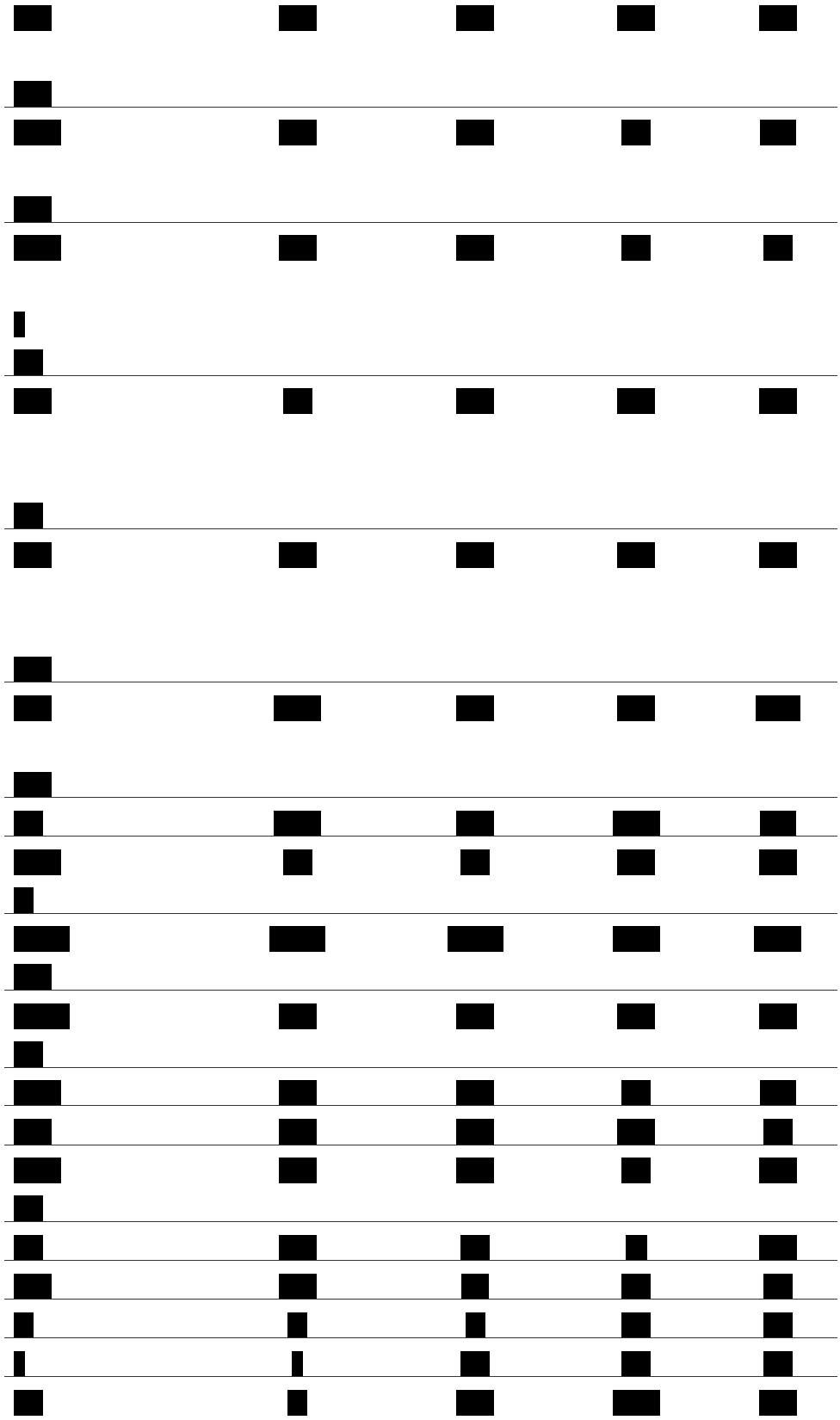


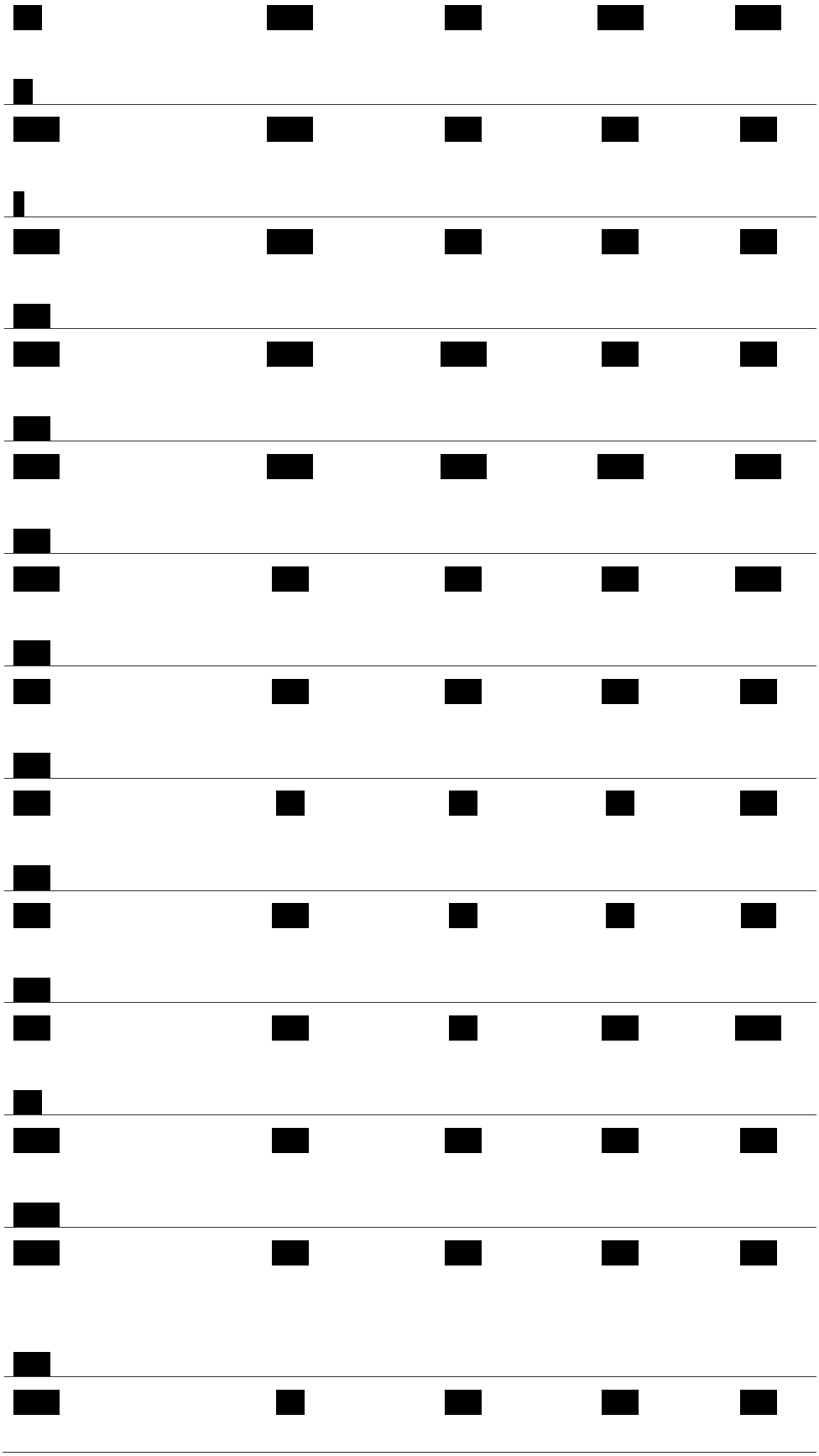


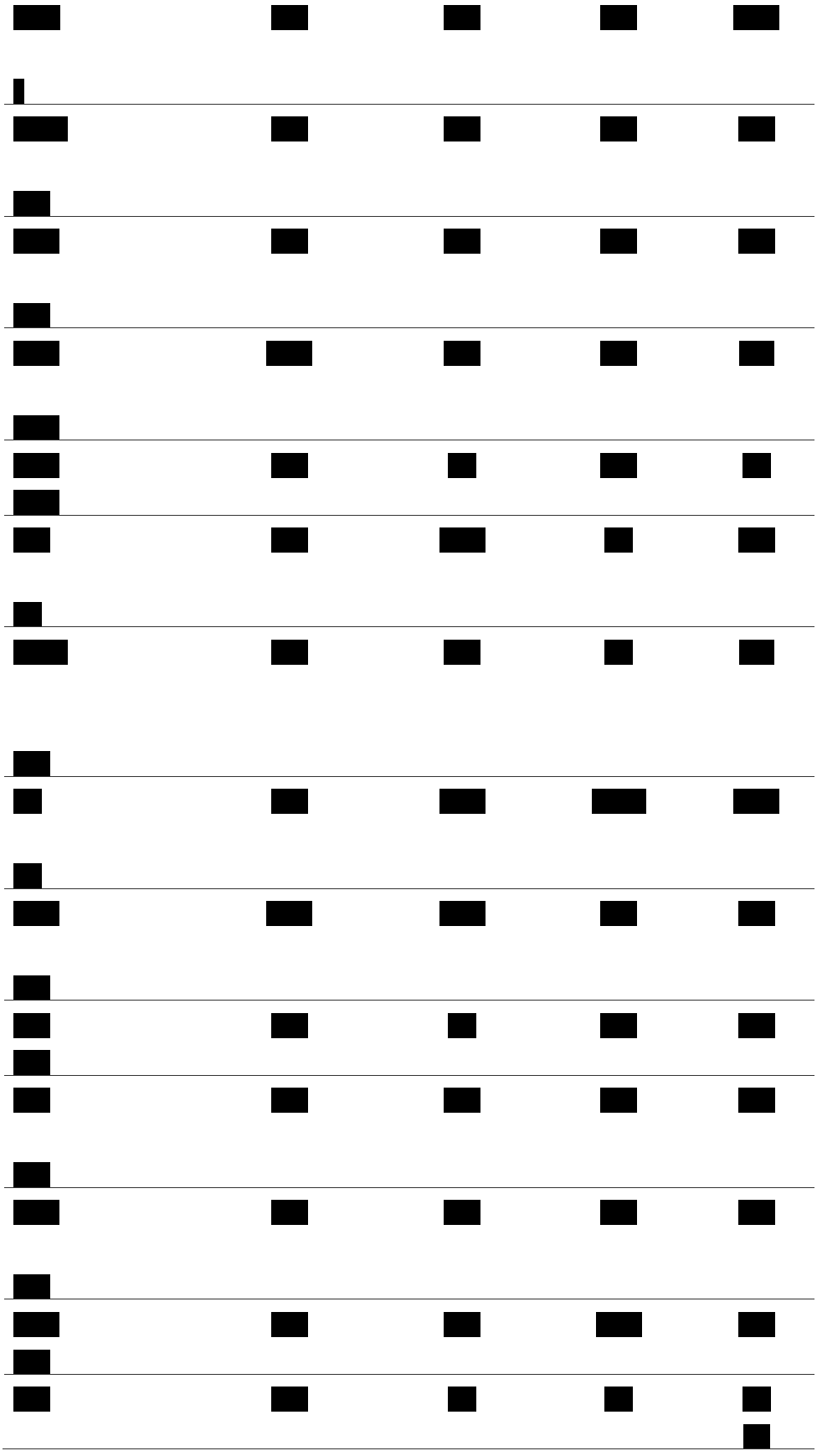


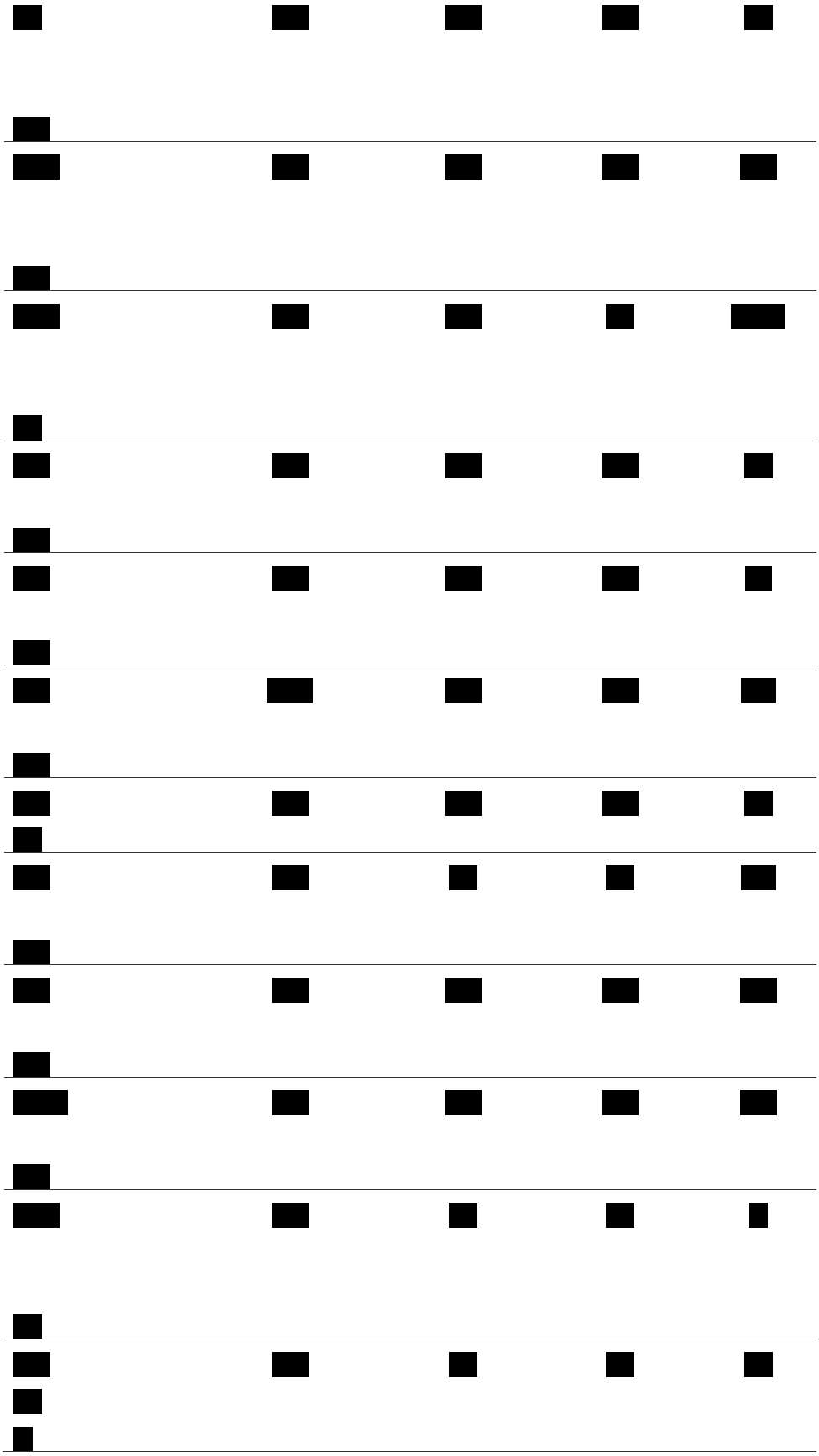


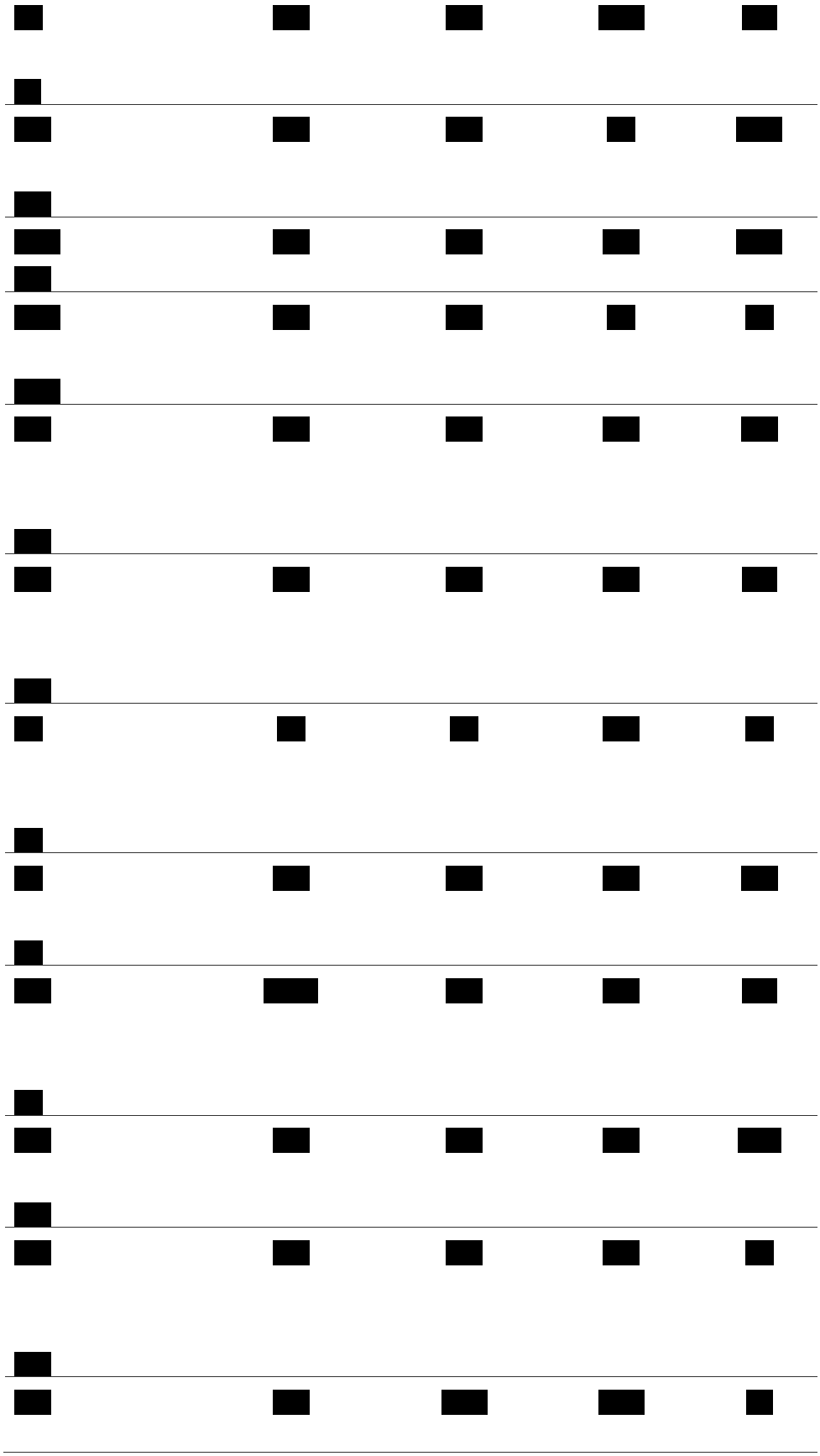


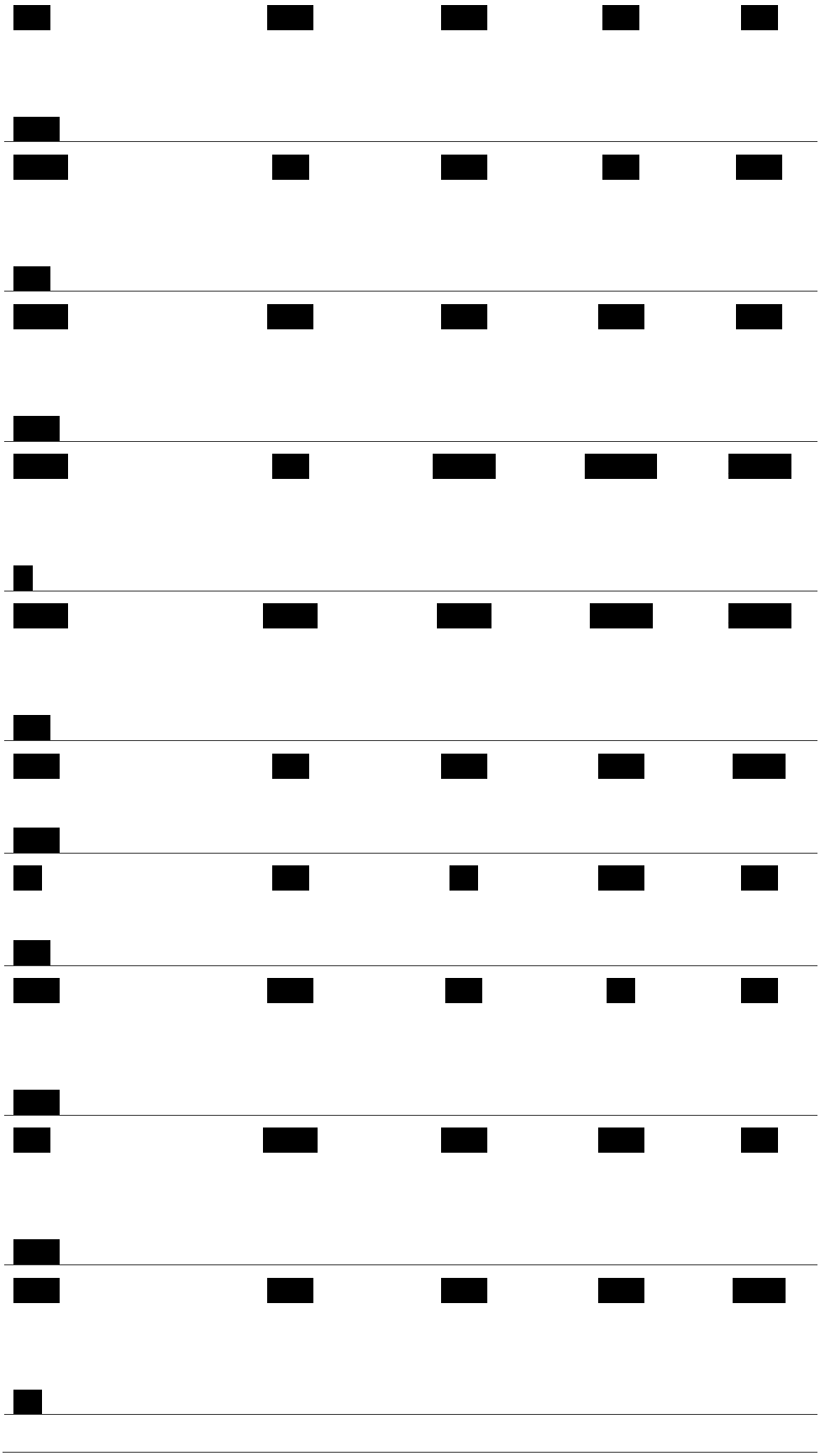


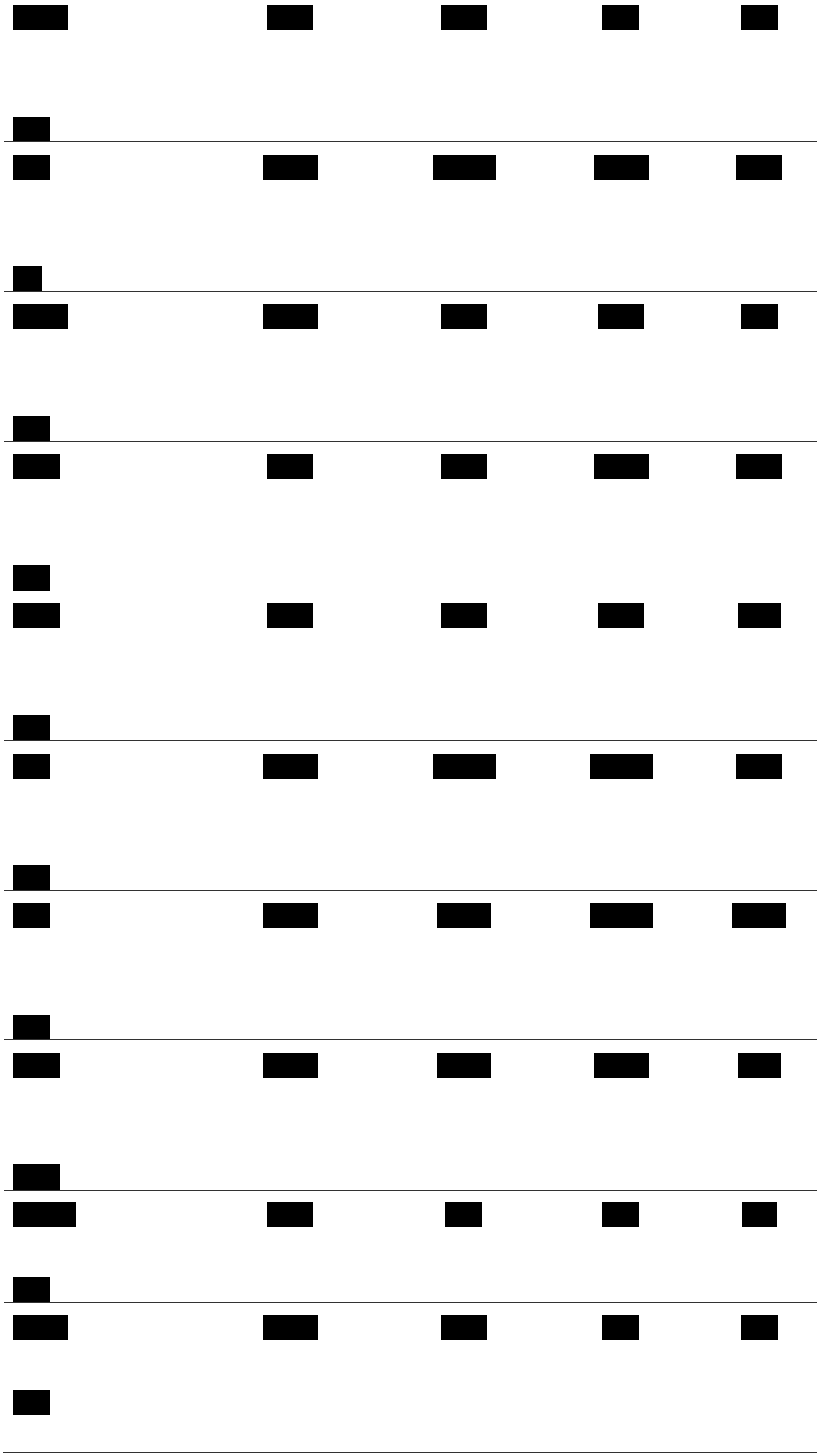


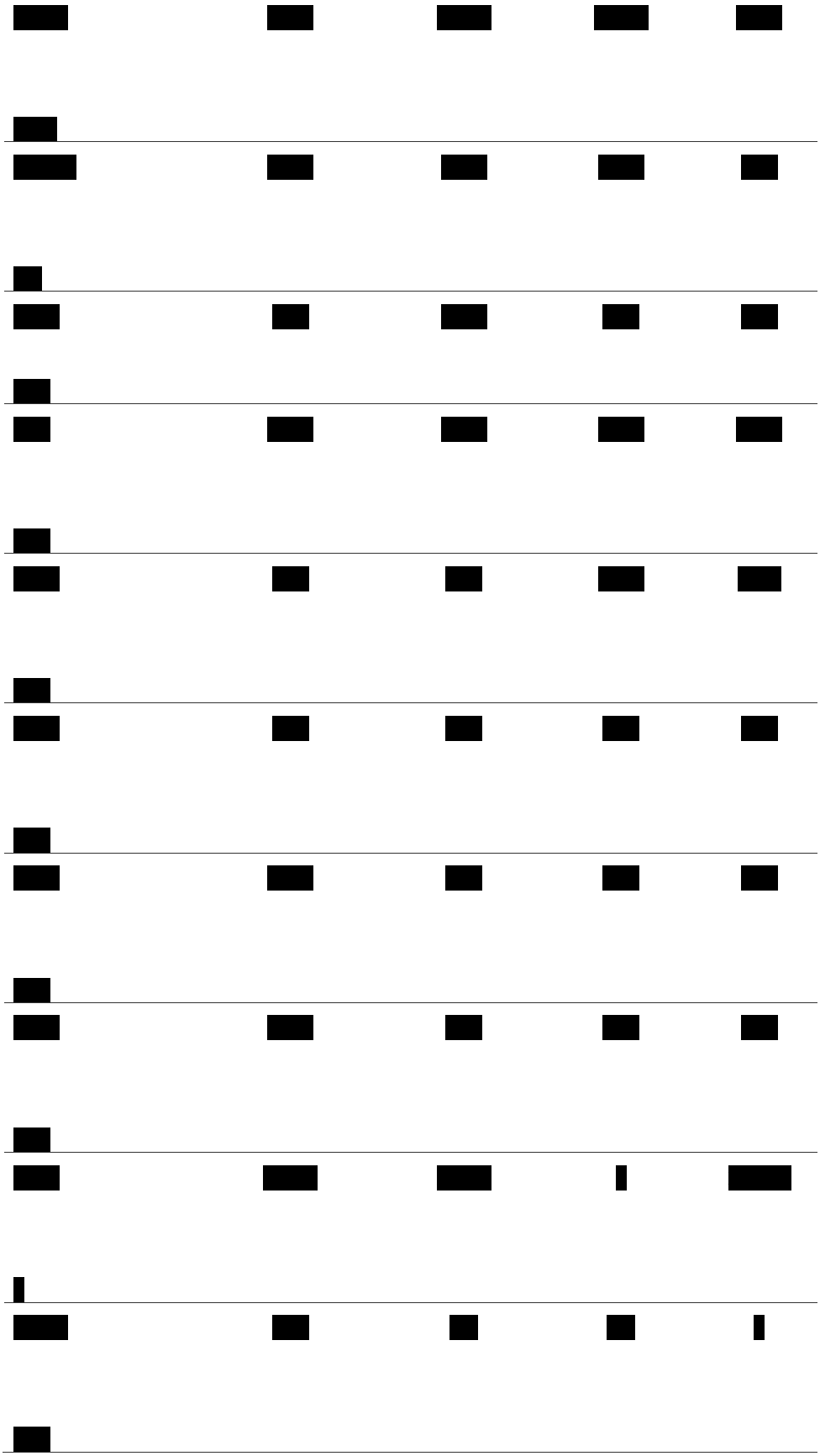


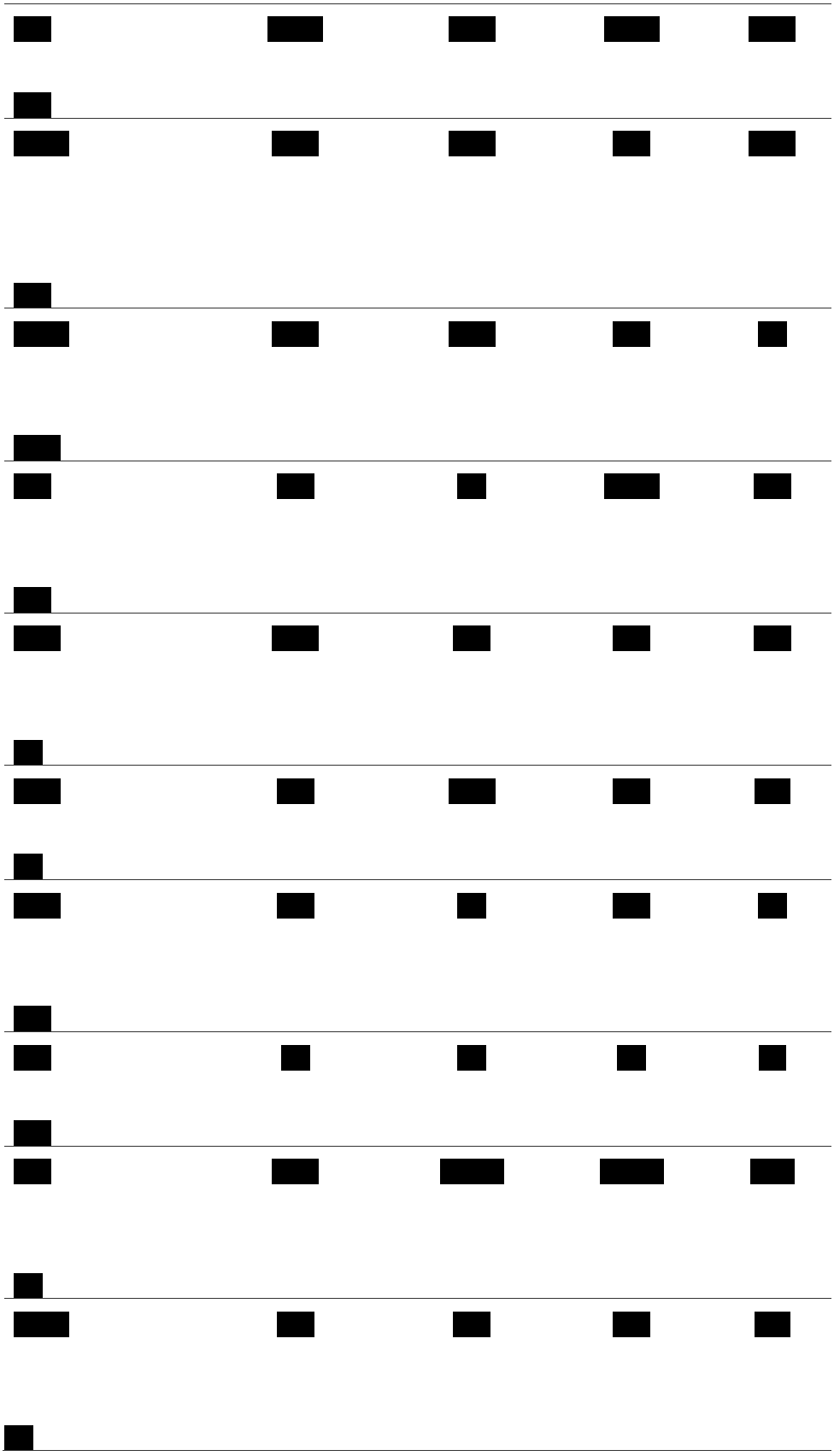


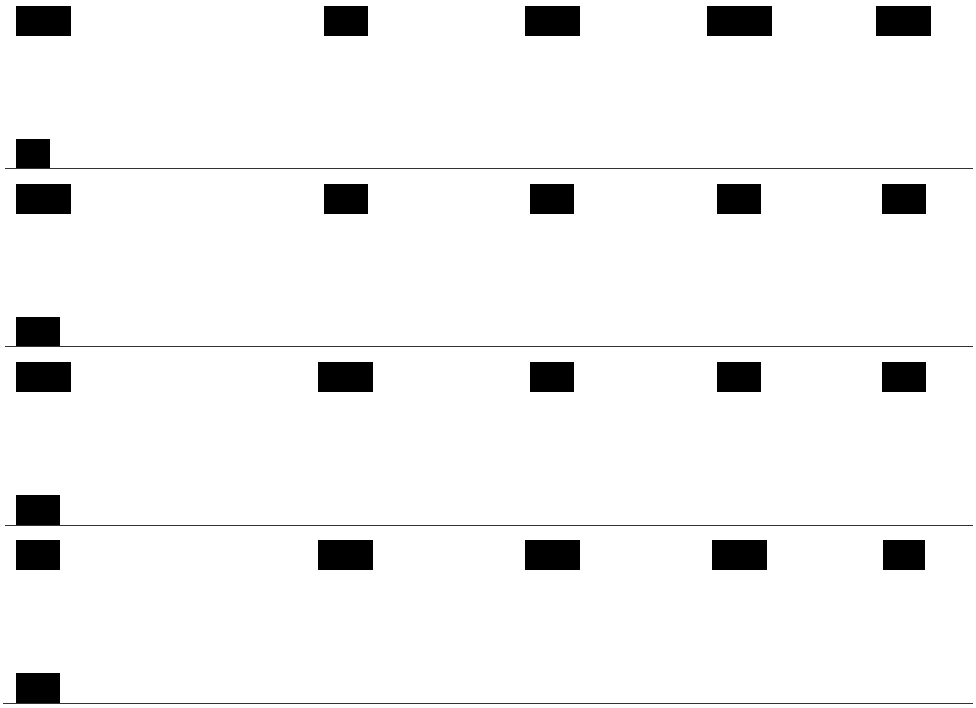












Appendix H. Literature searches for the clinical assessment

Efficacy and safety of the intervention and comparator(s)

The aim of this SLR was to identify and gather comprehensive clinical evidence (efficacy, safety, discontinuation and tolerability) about vamolorone for the treatment of Duchenne muscular dystrophy in boys aged 4 years and older.

As detailed in Table 69, Table 70, Table 71, the original clinical SLR search was conducted in July 2023 and an update to the same was conducted in March 2025. The searches were performed in the following indexed databases:

- Embase® (using Embase.com)
- MEDLINE®; MEDLINE In-Process (using PubMed.com)
- The Cochrane Library, including the following:
    - Cochrane Central Register of Controlled Trials (CENTRAL)

Table 69 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	https://www.embase.com/	Original SLR: Inception–July 2023 SLR update: January 2023–March 2025	Original SLR: 04.07.2023 SLR update: 10.03.2025
Medline	https://pubmed.ncbi.nlm.nih.gov/	Original SLR: Inception–July 2023 SLR update: January 2023–March 2025	Original SLR: 04.07.2023 SLR update: 10.03.2025
CENTRAL	https://www.cochranelibrary.com/advanced-search	Original SLR: Inception–June 2023 SLR update: January 2023–March 2025	Original SLR: 27.06.2023 SLR update: 10.03.2025

Abbreviations: CENTRAL = Cochrane Central Register of Controlled Trials, Embase = Excerpta Medica Database, MEDLINE = Medical Literature Analysis and Retrieval System Online, SLR = Systematic literature review.

Table 70 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
NICE	www.nice.org.uk	"duchenne muscular dystrophy"	12.03.2025
SMC	https://scottishmedicines.org.uk/	"duchenne muscular dystrophy"	12.03.2025

Abbreviations: NICE = National Institute for Health and Care Excellence, SMC = Scottish Medicines Consortium.

Conference abstracts from several relevant conference websites were captured in the Embase database searches. Additionally, two conferences (2023–2025 in SLR update) were searched for relevant abstracts. The following conferences were searched:

Table 71 Conference material included in the literature search (SLR update)

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
Muscular Dystrophy Association Scientific Conference	https://www.mdaconference.org/	Manual search	duchenne muscular dystrophy	19.03.2025
International Annual Congress of the World Muscle Society	https://www.worldmusclesociety.org/page/past-world-muscle-society-congresses	Manual search	duchenne muscular dystrophy	17.03.2025

Search strategies

The SLR was conducted based on PRISMA, Table 75 and generated from the research question pertinent to each selection.

The study selection process was performed by two independent reviewers based on a two-step approach: i) Abstracts/titles screening; ii) In-depth review of full-text articles.

First, titles and abstracts were screened by two independent reviewers for relevancy based on a predefined set of eligibility criteria (Table 75). Any discrepancy in study selection was resolved by consensus or with the help of a third reviewer. Relevant full-text citations were retrieved after abstract and title screening. Two reviewers independently assessed study eligibility, documenting exclusion reasons and discrepancies were resolved by a third reviewer.

After the records were identified and collected based on the search strategy, the references for all included records were stored in EndNote. The meta data and outcome data were collected and collated in MS Excel grid.

Table 72 Search strategy for Embase® (10th March 2025)

No.	Query	Results
#1	'duchenne muscular dystrophy'/syn OR 'duchenne muscular dystrophy' OR 'duchenne muscular dystrophy':ab,ti OR duchenne:ab,ti OR ((duchenne NEAR/3 dystrophy):ab,ti) OR 'duchenne muscular dystrophy'/exp	26525
#2	'vamorolone'/syn OR 'steroid'/exp OR 'vamorolone'/exp	2077957
#3	'randomization'/exp OR 'controlled clinical trial'/exp OR 'controlled clinical trial (topic)'/exp OR 'placebo effect'/exp OR 'placebo'/exp OR 'clinical trial'/exp OR 'clinical trial (topic)'/exp OR 'control group'/exp OR 'randomized controlled trial'/exp OR 'randomized controlled trial (topic)'/exp OR 'controlled clinical trial':ab,ti,kw OR 'controlled clinical trials':ab,ti,kw OR 'randomised controlled trial':ab,ti,kw OR 'randomized controlled trial':ab,ti,kw OR 'randomised controlled trials':ab,ti,kw OR 'randomized controlled trials':ab,ti,kw OR 'randomi?ed controlled trial*' OR rct:ab,ti,kw OR random*:ab,ti,kw OR ((random* NEAR/2 (alloca* OR assign* OR distribut* OR group*)):ab,ti,kw) OR (((single OR double OR triple OR treble) NEAR/2 (blind* OR mask*)):ab,ti,kw) OR placebo*:ab,ti,kw OR 'single blind procedure'/exp OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'triple blind procedure'/exp	3889091
#4	'single arm trial':ti,ab OR singl*:ti,ab OR 'single-arm':ti,ab OR 'single arm':ti,ab	2885506
#5	#3 OR #4	6364954
#6	#1 AND #2 AND #5	1106
#7	#1 AND #2 AND #5 AND [animals]/lim	100
#8	#6 NOT #7	1016
#9	#6 NOT #7 AND [english]/lim	1001
#10	#9 AND [2023-2025]/py	154

Table 73 Search strategy for MEDLINE® (10th March 2025)

No.	Query	Results
#1	duchenne muscular dystrophy[Title/Abstract]	12,269
#2	duchenne[Title/Abstract]	15,051
#3	duchenne muscular dystrophy[MeSH Terms]	7,823
#4	duchenne	16,395
#5	"duchenne dystrophy"[Tiab:~3]	13,972
#6	#1 OR #2 OR #3 OR #4 OR #5	16,395
#7	vamorolone[Supplementary Concept]	29
#8	steroid [MeSH Terms]	9,49,040
#9	vamorolone	57
#10	#7 OR #8 OR #9	9,49,063
#11	((((((((((((((((((((((((((randomization[MeSH Terms])) OR (controlled clinical trial[MeSH Terms])) OR (controlled clinical trial[Publication Type])) OR (placebo effect[MeSH Terms])) OR (placebo[MeSH Terms])) OR (clinical trial[MeSH Terms])) OR (clinical trial[Publication Type])) OR (control group[MeSH Terms])) OR (randomized controlled trial[MeSH Terms])) OR (randomized controlled trial[Publication Type])) OR (controlled clinical trial[Title/Abstract])) OR (controlled clinical trials[Title/Abstract])) OR (controlled clinical trials[Title/Abstract])) OR (randomized controlled trial[Title/Abstract])) OR (randomized controlled trial[Title/Abstract])) OR (randomized controlled trials[Title/Abstract])) OR (randomized controlled trials[Title/Abstract])) OR (randomized controlled trials[Title/Abstract])) OR (randomi?ed controlled trial*[Title/Abstract])) OR (RCT[Title/Abstract])) OR (random*[Title/Abstract])) OR (random*[Title/Abstract] NEAR/2 (alloca*[Title/Abstract] OR assign*[Title/Abstract] OR distribut*[Title/Abstract] OR group*[Title/Abstract]))))) OR (single[Title/Abstract])) OR (double[Title/Abstract])) OR (triple[Title/Abstract])) OR (treble[Title/Abstract]) OR (NEAR/2 (blind*[Title/Abstract] OR mask*[Title/Abstract])) OR placebo*[Title/Abstract] OR single blind procedure [MeSH Terms] OR crossover procedure [MeSH Terms] OR double blind procedure [MeSH Terms] OR triple blind procedure [MeSH Terms]	47,74,690
#12	(((single arm trial[Title/Abstract]) OR (singl*[Title/Abstract])) OR (single-arm[Title/Abstract])) OR (single arm[Title/Abstract])	22,67,299

No.	Query	Results
#13	#11 OR #12	48,44,852
#14	#6 AND #10 AND #13	162
#15	#6 AND #10 AND #13 AND (animal[Filter])	25
#16	#14 NOT #15	137
#17	#16 AND (2023:2025[pdat])	13

Table 74 Search strategy for Cochrane library (10th March 2025)

No.	Query	Results
#1	Muscular Dystrophy, Duchenne	991
#2	(duchenne muscular dystrophy or duchenne):ti,ab,kw	992
#3	duchenne near/3 dystrophy	984
#4	Vamorolone OR idebenone OR ataluren OR steroids	13959
#5	#1 or #2 or #3	1020
#6	#4 and #5	187
#7	#6 and Time frame: 2023-2025	16

Systematic selection of studies

Table 75 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Population	• Boys aged 4 years and older with DMD	• Studies that do include any other patients/populations • Mixed adult and child populations	No change
Intervention	• Vamorolone • Glucocorticoids	• Any other intervention/comparator	No change
Comparators	• Best supportive care* • Placebo*	NA	Glucocorticoids only

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Outcomes	• Walking ability (ambulation) • Time to stand • Muscle function • Growth patterns • Bone metabolism • Vertebral fractures • Endocrine function • Behavioural changes • Ability to undertake activities of daily living • Adverse effects of treatment	• No reported outcomes of interest	• Time to stand • Growth patterns Adverse effects of treatment
Study design	• RCTs, including single-arm extensions • Single-arm trials	• Non-RCTs • Observational studies (including patient registries) • Cross-sectional studies • Animal studies • In vitro/ex vivo studies • Individual case study reports • Systematic literature reviews**	• [redacted]RCTs
Publication type	• Article, conference abstract, conference paper, article in press	• Short survey • Reviews • Letters • Comment articles • Notes	No change
Language restrictions	• English	• Non-English	No change
Date	• No restrictions	NA	2017 and onwards

*Only included if compared to an active comparator listed; **SLRs will be checked for any additional relevant studies.

DMD – Duchenne Muscular Dystrophy; RCT – Randomized controlled trials; SLR – Systematic literature review.

The PRISMA flow diagram of the clinical SLR is presented in **Error! Reference source not found.**. The clinical SLR update identified a total of 153 records from three biomedical databases—Embase, MEDLINE, and Cochrane—using the search strategies outlined in Table 72, Table 73, and Table 74. Deduplication resulted in 134 titles/abstracts being screened by two independent reviewers. One trial was retrieved from trial registers. Title and abstract screening led to inclusion of 17 publications which were thoroughly reviewed by two independent reviewers using full-text articles to confirm their inclusion. Of these, eight were included based on the pre-defined PICOS criteria (see Table 75). Grey literature

from relevant conferences, NICE and SMC, and bibliographic search within relevant SLRs led to inclusion of 10 records. Therefore, a total of 18 records were included for two unique studies in the SLR update.

Based on the original SLR and the current SLR update, a total of 46 reports (28 from the original SLR and 18 from the SLR update) were included in the review. Of these, 16 unique studies were identified.

Of these 16 studies, two were considered relevant for use in this submission. The studies are described in Table 76.

Figure 22 PRISMA flow diagram for Clinical SLR update

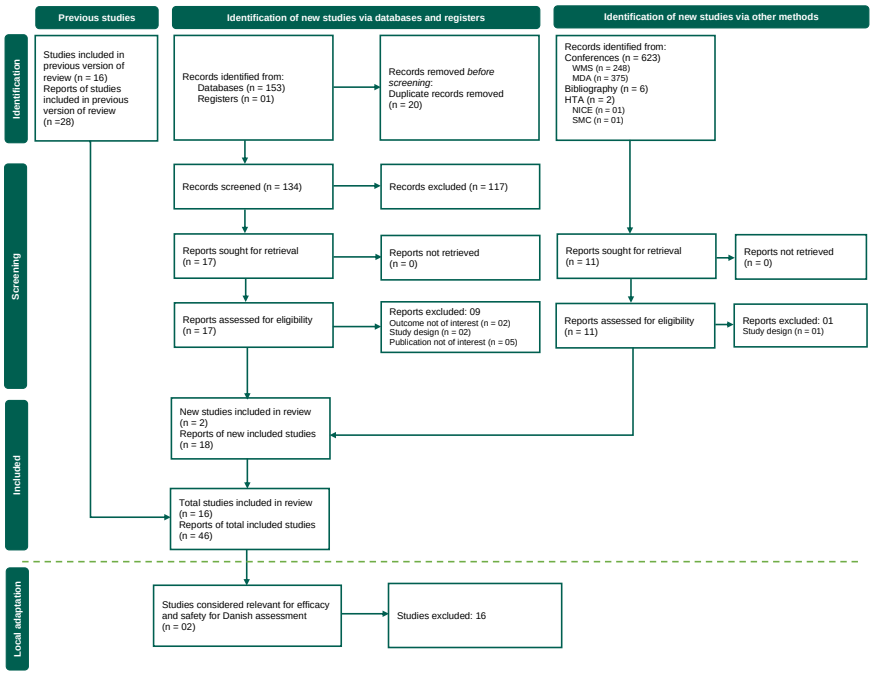


Table 76 Overview of study design for studies included in the analyses

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
VISION-DMD [17]	To determine if vamorolone, a structurally unique dissociative steroidal anti-inflammatory drug, is able to retain efficacy while reducing safety concerns with use in Duchenne muscular dystrophy (DMD)	Randomized Clinical Trial	Boys 4 to younger than 7 years of age with DMD were enrolled	vamorolone, 2 mg/kg per day (n=30); vamorolone, 6 mg/kg per day (n=28); Placebo (n=28); prednisone, 0.75 mg/kg per day (n=31)	Time to stand from supine velocity (TTSTAND), 6-minute walk test (6MWT), Time to run/ walk 10 m (TTRW), Time to climb 4 stairs (TTCLIMB) NorthStar Ambulatory Assessment (NSAA) Handheld myometry (elbow flexors, knee extensors). Pediatric Outcomes Data Collection Instrument (PODCI)	

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
					Psychosocial Adjustment and Role Skills Scale III (PARS III) Treatment Satisfaction Questionnaire (TSQM). Safety end points	
FOR-DMD [5]	To compare efficacy and adverse effects of the 3 most frequently prescribed corticosteroid regimens in boys with Duchenne muscular dystrophy.	Randomized Clinical Trial	Boys with genetically confirmed DMD aged 4 years to younger than 8 years at the time of screening were eligible	Daily deflazacort (0.90mg/kg) (n = 65), Daily prednisone (0.75mg/kg) (n = 65), or intermittent prednisone (0.75mg/kg for 10 days on and then 10 days off) (n = 66)	The composite primary outcome comprised 3 end points (each averaged across all follow-up visits after baseline through month 36): (1) rise from the floor velocity (reciprocal of time to rise from the floor in rise/seconds); (2) forced vital capacity (in liters); and (3) participant or parent global satisfaction with treatment measured by the Treatment Satisfaction	10-m walk or run velocity North Star Ambulatory Assessment total score Distance for the 6-minute walk test TSQM effectiveness subscale score Ankle range of motion Quality-of-life scores Cardiac function (left ventricular ejection fraction and fractional

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
					Questionnaire for Medication (TSQM; score range, 0-100)	shortening as measured by echocardiography)

Excluded fulltext references

Table 77 Overview of studies excluded in the technology assessment

Publication	Exclusion reason
Deflazacort dose optimization and safety evaluation in Duchenne muscular dystrophy (DOSE): A randomized, double-blind non-inferiority trial. European Journal of Paediatric Neurology 2022; 38	Wrong comparator
Intermittent versus daily regimen of prednisolone in ambulatory boys with Duchenne muscular dystrophy: A randomized, open-label trial. Muscle and Nerve. 2022;65(1):60-66.	Wrong comparator
Efficacy and safety of deflazacort vs prednisone and placebo for Duchenne muscular dystrophy. Neurology. 2016;87(20):2123-2131.	Published prior to 2017
Daily prednisone treatment in duchenne muscular dystrophy in southwest china. Muscle and Nerve. 2015;52(6):1001-1007.	Published prior to 2017
Randomized, blinded trial of weekend vs daily prednisone in Duchenne muscular dystrophy. Neurology. 2011;77(5):444-452.	Published prior to 2017
Intermittent prednisone therapy in Duchenne muscular dystrophy: A randomized controlled trial. Archives of Neurology. 2005;62(1):128-132.	Published prior to 2017
A multicenter, double-blind, randomized trial of deflazacort versus prednisone in duchenne muscular dystrophy. Muscle and Nerve. 2000;23(9):1344-1347.	Published prior to 2017
Deflazacort vs. prednisone in Duchenne muscular dystrophy: Trends of an ongoing study. Brain and Development. 1995;17:39-43.	Published prior to 2017
Low-dose prednisolone treatment in Duchenne and Becker muscular dystrophy. Neuromuscular Disorders. 1995;5(3):233-241.	Published prior to 2017
Duchenne dystrophy: Randomized, controlled trial of prednisone (18 months) and azathioprine (12 months). Neuromuscular Disorders. 1993;43(3):520-527.	Published prior to 2017
Steroids in Duchenne muscular dystrophy - Deflazacort trial. Neurology. 1991;1(4):261-266.	Published prior to 2017
Randomized, double-blind six-month trial of prednisone in Duchenne's muscular dystrophy. New England Journal of Medicine. 1989;320(24):1592-1597.	Published prior to 2017
Prednisone in Duchenne dystrophy: A randomized, controlled trial defining the time course and dose response. Archives of Neurology. 1991;48(4):383-388.	Published prior to 2017
Deflazacort in Duchenne dystrophy: study of long-term effect. Muscle & nerve. 1994;17(4)386-391.	Published prior to 2017

Quality assessment

Two publications presenting RCT data from the VISION-DMD and FOR-DMD trial underwent a quality assessment (QA) using the QA checklist from the NICE Single Technology Assessment manufacturer submission template for randomized controlled trials (Table 78).

Table 78 NICE Checklist for RCTs

Question	Response options	VISION-DMD	FOR-DMD
Was randomization carried out appropriately?	Yes/No/Unclear	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes/No/Unclear	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes/No/Unclear	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes/No/Unclear	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	Yes/No/Unclear	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Yes/No/Unclear	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes/No/Unclear	No	No
Also consider whether the authors of the study publication declared any conflicts of interest	Yes/No/Unclear	Yes	Yes

Unpublished data

N/A

Appendix I. Literature searches for health-related quality of life

Health-related quality-of-life search

The aim of this SLR was to identify and gather comprehensive HRQoL evidence (including utility, disutility and decrements) for the treatment of patients with DMD and their caregivers.

As detailed in Table 79, Table 80, and Table 81 the utility and HRQoL SLR search was conducted in 2017,followed by an update in 2019, 2023 and 2025. The searches were performed in the following indexed databases:

- Embase® (using Embase.com)
- MEDLINE®; MEDLINE In-Process (using PubMed.com)
- The Cochrane Library, including the following:
    - Cochrane Central Register of Controlled Trials (CENTRAL)
- EuroQoL

Table 79 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	https://www.embase.com/	Original SLR: Inception–2017 SLR updates: 2019, 2023 and 2025	Current SLR update: 10.03.2025
Medline	https://pubmed.ncbi.nlm.nih.gov/	Original SLR: Inception–2017 SLR updates: 2019, 2023 and 2025	Current SLR update: 10.03.2025
CENTRAL	https://www.cochranelibrary.com/advanced-search	Original SLR: Inception–2017 SLR updates: 2019, 2023 and 2025	Current SLR update: 10.03.2025
EuroQoL	https://euroqol.org/research-at-euroqol/fair-principles-saved-data-repository/	Original SLR: Inception–2017 SLR updates: 2019, 2023 and 2025	Current SLR update: 10.03.2025

Abbreviations: CENTRAL = Cochrane Central Register of Controlled Trials, Embase = Excerpta Medica Database, MEDLINE = Medical Literature Analysis and Retrieval System Online, SLR = Systematic literature review.

Table 80 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
NICE	www.nice.org.uk		12.03.2025
SMC	https://scottishmedicines.org.uk/		12.03.2025

Abbreviations: NICE = National Institute for Health and Care Excellence, SMC = Scottish Medicines Consortium.

Table 81 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
Muscular Dystrophy Association Scientific Conference	https://www.mdaconference.org/	Manual search	duchenne muscular dystrophy	19.03.2025
International Annual Congress of the World Muscle Society	https://www.worldmusclesociety.org/page/past-world-muscle-society-congresses	Manual search	duchenne muscular dystrophy	17.03.2025

Search strategies

The SLR was conducted based on PRISMA, Table 86 and generated from the research question pertinent to each selection.

The study selection process was performed by two independent reviewers based on a two-step approach: i) Abstracts/titles screening; ii) In-depth review of full-text articles.

First, titles and abstracts were screened by two independent reviewers for relevancy based on a predefined set of eligibility criteria (Table 86). Any discrepancy in study selection was resolved by consensus or with the help of a third reviewer. Relevant full-text citations were retrieved after abstract and title screening. Two reviewers independently assessed study eligibility, documenting exclusion reasons and discrepancies were resolved by a third reviewer.

After the records were identified and collected based on the search strategy, the references for all included records were stored in EndNote. The meta data and outcome data were collected and collated in MS Excel grid.

Table 82 Search strategy for Embase® (10th March 2025)

No.	Query	Results
#1	'duchenne muscular dystrophy'/syn OR 'duchenne muscular dystrophy' OR 'duchenne muscular dystrophy':ab,ti OR duchenne:ab,ti OR ((duchenne NEAR/3 dystrophy):ab,ti) OR 'duchenne muscular dystrophy'/exp	26525
#2	('utility':ab,ti,kw OR 'utilities':ab,ti,kw OR 'disutility':ab,ti,kw OR 'disutilities':ab,ti,kw OR 'sf 6':ab,ti,kw OR sf6:ab,ti,kw OR 'short form 6':ab,ti,kw OR 'shortform 6':ab,ti,kw OR 'sf six':ab,ti,kw OR sfsix:ab,ti,kw OR 'shortform six':ab,ti,kw OR 'short form six':ab,ti,kw OR euroqol:ab,ti,kw OR 'euro qol':ab,ti,kw OR 'euro-qol':ab,ti,kw OR 'euroqol 5d':ab,ti,kw OR 'euroqol-5d':ab,ti,kw OR 'euroqol 5-d':ab,ti,kw OR eq5d:ab,ti,kw OR 'eq 5d':ab,ti,kw OR 'health utilit* index':ab,ti,kw OR hui:ab,ti,kw OR hui1:ab,ti,kw OR hui2:ab,ti,kw OR 'hui-2':ab,ti,kw OR hui3:ab,ti,kw OR 'hui-3':ab,ti,kw OR 'standard gamble*':ab,ti,kw OR ((standard NEAR/2 gamble*):ab,ti,kw) OR 'time trade off':ab,ti,kw OR 'time tradeoff':ab,ti,kw OR timetradeoff*:ab,ti,kw OR tto:ab,ti,kw OR ((time NEAR/2 trade*):ab,ti,kw) OR hsuv*:ab,ti,kw OR 'health* year* equivalent*':ab,ti,kw OR (('health state' NEAR/2 (utility* OR disutility* OR preferen* OR valu*)):ab,ti,kw) OR 'psychometry'/exp OR 'quality adjusted life year'/exp OR 'quality adjusted life':ab,ti,kw OR qaly*:ab,ti,kw OR qald*:ab,ti,kw OR qale*:ab,ti,kw OR qtime*:ab,ti,kw OR 'disability adjusted life year':ab,ti,kw OR 'disability adjusted life years':ab,ti,kw OR daly*:ab,ti,kw OR 'duchenne muscular dystrophy-quality of life':ab,ti,kw OR 'duchenne muscular dystrophy-health index':ab,ti,kw OR 'dmd-hi':ab,ti,kw OR 'duchenne muscular dystrophy caregiver reported-health index':ab,ti,kw OR 'dmdcr-hi':ab,ti,kw OR 'zarit caregiver burden interview':ab,ti,kw OR 'zbi':ab,ti,kw OR 'patient-reported outcomes measurement information system':ab,ti,kw OR 'promis':ab,ti,kw) AND [2015-2025]/py	366713
#3	#1 AND #2	416
#4	#1 AND #2 AND ([editorial]/lim OR [letter]/lim OR [note]/lim OR [review]/lim OR [short survey]/lim) AND [animals]/lim	5
#5	#4 NOT #5	411
#6	#5 AND [2023-2025]/py	137

Table 83 Search strategy for MEDLINE® (10th March 2025)

No.	Query	Results
#1	duchenne muscular dystrophy[Title/Abstract]	12286
#2	duchenne[Title/Abstract]	15069

#3	duchenne muscular dystrophy[MeSH Terms]	7836
#4	duchenne	16413
#5	"duchenne dystrophy"[Tiab:~3]	13989
#6	#1 OR #2 OR #3 OR #4 OR #5	16413
#7	utility[Title/Abstract] OR utilities[Title/Abstract] OR disutility[Title/Abstract] OR disutilities[Title/Abstract] OR SF6[Title/Abstract] OR sf6[Title/Abstract] OR short form6[Title/Abstract] OR shortform 6[Title/Abstract] OR sfsix[Title/Abstract] OR sfsix[Title/Abstract] OR short form six[Title/Abstract] OR short form six[Title/Abstract] OR euroqol[Title/Abstract] OR euro qol[Title/Abstract] OR euro qol[Title/Abstract] OR euroqol 5d[Title/Abstract] OR euroqol 5d[Title/Abstract] OR euroqol 5 d[Title/Abstract] OR eq5d[Title/Abstract] OR eq 5d[Title/Abstract] OR health utility index[Title/Abstract] OR hui[Title/Abstract] OR hui1[Title/Abstract]OR hui2[Title/Abstract] OR hui 2[Title/Abstract] OR hui3[Title/Abstract] OR hui 3[Title/Abstract] OR standard gamble[Title/Abstract] OR (standard[Title/Abstract] NEAR/2 gamble[Title/Abstract]) OR time trade off[Title/Abstract] OR time trade off[Title/Abstract] OR time trade off[Title/Abstract] OR tto[Title/Abstract] OR (time[Title/Abstract] NEAR/2 trade[Title/Abstract]) OR hsuv[Title/Abstract] OR health year equivalent[Title/Abstract] OR (health state[Title/Abstract] NEAR/2(utility[Title/Abstract] OR disutility[Title/Abstract] OR preference[Title/Abstract] OR value[Title/Abstract])) OR psychometry[All fields] OR quality adjusted life year[MeSH Terms] OR quality adjusted life[Title/Abstract] OR qaly[Title/Abstract] OR qald[Title/Abstract] OR qale[Title/Abstract] OR qtime[Title/Abstract] OR disability adjusted life year[Title/Abstract] OR disability adjusted life years[Title/Abstract] OR daly[Title/Abstract] OR Pediatric Quality of Life Inventory for DMD[Title/Abstract]OR PedsQL DMD[Title/Abstract] OR Children's Depression Inventory 2nd Edition[Title/Abstract] OR CDI 2[Title/Abstract] OR Duchenne Muscular Dystrophy Health Index[Title/Abstract] OR DMD HI[Title/Abstract] OR Duchenne Muscular Dystrophy Caregiver Reported Health Index[Title/Abstract] OR DMDCR HI[Title/Abstract] OR Zarit Caregiver Burden Interview[Title/Abstract] OR ZBI[Title/Abstract] OR Patient Reported Outcomes Measurement Information System[Title/Abstract] OR PROMIS[Title/Abstract]	360861
#8	("utility"[Title/Abstract] OR "utilities"[Title/Abstract] OR "disutility"[Title/Abstract] OR "disutilities"[Title/Abstract] OR "SF6"[Title/Abstract] OR "SF6"[Title/Abstract] OR (("short"[All Fields] OR "shorts"[All Fields]) AND "form6"[Title/Abstract]) OR ("shortform"[All Fields] AND "6"[Title/Abstract]) OR "sfsix"[Title/Abstract] OR "sfsix"[Title/Abstract] OR "short form six"[Title/Abstract] OR "short form six"[Title/Abstract] OR "euroqol"[Title/Abstract] OR "euro qol"[Title/Abstract] OR "euro qol"[Title/Abstract] OR "euroqol 5d"[Title/Abstract] OR "euroqol 5d"[Title/Abstract] OR "euroqol 5 d"[Title/Abstract] OR "eq5d"[Title/Abstract] OR "eq 5d"[Title/Abstract] OR "health utility index"[Title/Abstract] OR "hui"[Title/Abstract] OR "hui1"[Title/Abstract] OR "hui2"[Title/Abstract] OR "hui 2"[Title/Abstract]	217724

	OR "hui3"[Title/Abstract] OR "hui 3"[Title/Abstract] OR "standard gamble"[Title/Abstract] OR ("standard"[Title/Abstract] AND ("near 2"[All Fields] AND "gamble"[Title/Abstract])) OR "time trade off"[Title/Abstract] OR "time trade off"[Title/Abstract] OR "time trade off"[Title/Abstract] OR "tto"[Title/Abstract] OR ("time"[Title/Abstract] AND ("NEAR"[All Fields] AND "2 trade"[Title/Abstract])) OR "hsuv"[Title/Abstract] OR (("Health"[MeSH Terms] OR "Health"[All Fields] OR "health s"[All Fields] OR "healthful"[All Fields] OR "healthfulness"[All Fields] OR "healths"[All Fields]) AND "year equivalent"[Title/Abstract]) OR (("health state"[Title/Abstract] AND "near 2"[All Fields]) AND ("utility"[Title/Abstract] OR "disutility"[Title/Abstract] OR "preference"[Title/Abstract] OR "value"[Title/Abstract])) OR "psychometry"[All Fields] OR "quality adjusted life years"[MeSH Terms] OR "quality adjusted life"[Title/Abstract] OR "qaly"[Title/Abstract] OR "qald"[Title/Abstract] OR "qale"[Title/Abstract] OR "qtime"[Title/Abstract] OR "disability adjusted life year"[Title/Abstract] OR "disability adjusted life years"[Title/Abstract] OR "daly"[Title/Abstract] OR ((("paediatrics"[All Fields] OR "pediatrics"[MeSH Terms] OR "pediatrics"[All Fields] OR "paediatric"[All Fields] OR "pediatric"[All Fields]) AND ("quality of life"[MeSH Terms] OR ("quality"[All Fields] AND "life"[All Fields]) OR "quality of life"[All Fields]) AND ("inventoried"[All Fields] OR "inventory s"[All Fields] OR "inventorying"[All Fields] OR "personality inventory"[MeSH Terms] OR ("personality"[All Fields] AND "Inventory"[All Fields]) OR "personality inventory"[All Fields] OR "inventories"[All Fields] OR "equipment and supplies"[MeSH Terms] OR ("equipment"[All Fields] AND "supplies"[All Fields]) OR "equipment and supplies"[All Fields] OR "Inventory"[All Fields])) AND "for dmd"[Title/Abstract]) OR "pedsql dmd"[Title/Abstract] OR (("child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields] OR "child s"[All Fields] OR "children s"[All Fields] OR "childrens"[All Fields] OR "childs"[All Fields]) AND "depression inventory 2nd edition"[Title/Abstract]) OR "cdi 2"[Title/Abstract] OR (("duchenne"[All Fields] OR "duchenne s"[All Fields] OR "duchennes"[All Fields]) AND "muscular dystrophy health index"[Title/Abstract]) OR ("DMD"[All Fields] AND "HI"[Title/Abstract]) OR ((("muscular dystrophy, duchenne"[MeSH Terms] OR ("Muscular"[All Fields] AND "Dystrophy"[All Fields] AND "duchenne"[All Fields]) OR "duchenne muscular dystrophy"[All Fields] OR ("duchenne"[All Fields] AND "Muscular"[All Fields] AND "Dystrophy"[All Fields])) AND ("caregiver s"[All Fields] OR "caregivers"[MeSH Terms] OR "caregivers"[All Fields] OR "Caregiver"[All Fields] OR "caregiving"[All Fields]) AND ("reportable"[All Fields] OR "reporting"[All Fields] OR "reportings"[All Fields] OR "research report"[MeSH Terms] OR ("research"[All Fields] AND "report"[All Fields]) OR "research report"[All Fields] OR "report"[All Fields] OR "Reported"[All Fields] OR "reports"[All Fields])) AND "health index"[Title/Abstract]) OR ("DMDCR"[All Fields] AND "HI"[Title/Abstract]) OR "zarit caregiver burden interview"[Title/Abstract] OR "ZBI"[Title/Abstract] OR "patient reported outcomes measurement information system"[Title/Abstract] OR "PROMIS"[Title/Abstract]) AND (2015:2025[pdat])	
#9	#6 AND #8	164
#10	#6 AND #8 AND (animal[Filter])	26

#11	#9 NOT #10	138
#12	#11 AND (2023:2025[pdat])	47

Table 84 Search strategy for Cochrane library (10th March 2025)

No.	Query	Results
#1	Muscular Dystrophy, Duchenne	991
#2	(duchenne muscular dystrophy or duchenne):ti,ab,kw	992
#3	duchenne near/3 dystrophy	984
#4	Vamorolone OR idebenone OR ataluren OR steroids	13959
#5	#1 or #2 or #3	1020
#6	#4 and #5	187
#7	#6 and Time frame: 2023-2025	16

Table 85 Search strategy for EuroQol (10th March 2025)

No.	Query	Results
#1	"duchenne muscular dystrophy" or duchenne	0

Inclusion and exclusion criteria used for assessment of studies are presented in Table 86.

Table 86 Inclusion and exclusion criteria used for assessment of studies (utility and HRQoL studies)

	Inclusion criteria	Exclusion criteria
Population	• Patients with DMD • Carers of patients with DMD	• Studies that include any other patients/populations
Intervention/ comparators	• Any intervention for the treatment of DMD	• None
Outcomes	• Utility scores measured using generic or (e.g. EQ-5D, HUI, SF-6D, CHU-9D) or disease specific tools (e.g. DMD-QoL)	• No reported outcomes of interest

	Inclusion criteria	Exclusion criteria
	• Disutilities measured using generic either specific (e.g. DMD-QoL) • Quality of life scales like Duchenne Muscular Dystrophy-Health Index (DMD-HI), Duchenne Muscular Dystrophy Caregiver Reported-Health Index (DMDCR-HI), Zarit Caregiver Burden Interview ('ZBI), Patient-Reported Outcomes Measurement Information System (PROMIS)	
Study type	• RCTs • Non-RCTs • Observational studies • Economic evaluations: ▪ Cost-utility analysis ▪ Economic evaluation alongside clinical trials (EEACT)	• Individual case studies (reports/series)
Publication type	• Article, conference abstract, conference paper, article in press	• Short survey • Reviews • Letters • Comment articles • Systematic literature reviews*
Language restrictions	• English	• Non-English
Date	• No restrictions	NA

*SLRs will be checked for any additional relevant studies.

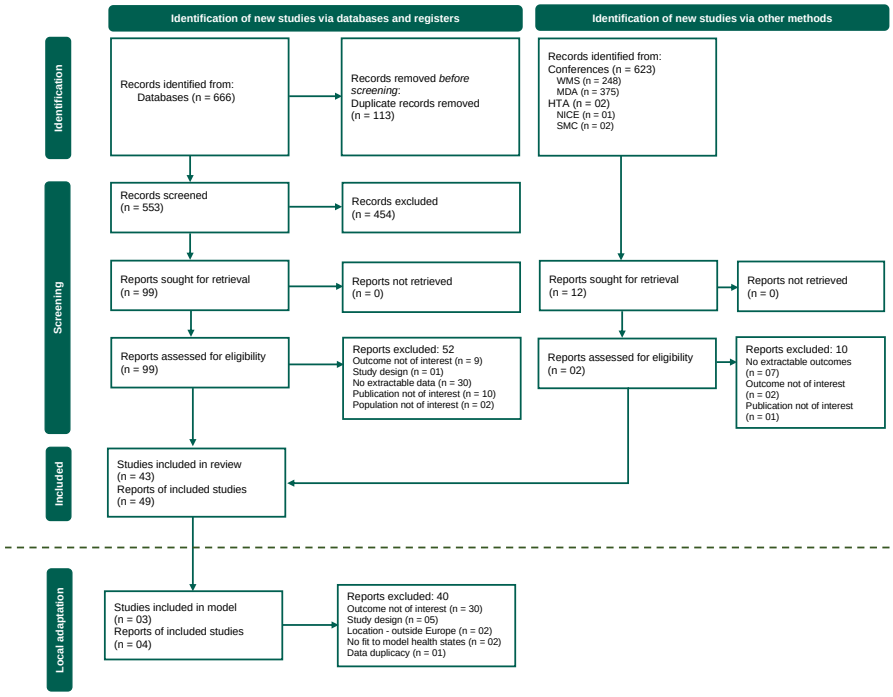
CHU-9D – Child Health Utility 9-Dimension; DMD – Duchenne Muscular Dystrophy; EEACT – Economic evaluation alongside clinical trials; EQ-5D – EuroQoL 5-Dimension; HRQoL – Health-related quality of life; HUI – Health Utilities Index; RCT – Randomised controlled trials; SLR – Systematic literature review; SF-6D – Short Form 6-Dimension.

The PRISMA flow diagram of the economic SLR for HRQol and utility is presented in Figure 23. The clinical SLR update conducted in 2025 identified a total of 200 records from three biomedical databases—Embase, MEDLINE, and Cochrane—using the search strategies outlined in Table 82, Table 83, and Table 84. Deduplication resulted in 158 titles/abstracts being screened by two independent reviewers. Title and abstract screening led to inclusion of 34 publications which were thoroughly reviewed by two independent reviewers using full-text articles to confirm their inclusion. Of these, 25 were included based on the pre-

defined PICOS criteria (see Table 86). Grey literature from relevant conferences, NICE and SMC, and bibliographic search within relevant SLRs led to the inclusion of three records. Therefore, a total of 28 records were included for 25 unique studies in the current SLR update.

Based on the previous SLR conducted in 2017 followed by SLR updates conducted in 2017, 2019 and 2023 along with the current SLR update, a total of 50 reports were included in the review. Of these, 46 unique studies were identified.

Figure 23 PRISMA flow diagram of HRQoL and Utility update



Overview of studies included in SLR

Table 87 Studies included in the SLR and model with reasons for exclusion of studies from model

Reference	Inclusion in Model	Reason for exclusion
Szabo SM, Audhya IF, Bever A, Sun R, Griffin E, Feeny D, Malone D, Neumann P, Iannaccone ST, Gooch KL. PCR42 Health State Utilities in Duchenne Muscular Dystrophy (DMD): A Longitudinal Study Using the EQ5D and Health Utilities Index (HUI). Value in Health. 2024 Jun 1;27(6):S303.	Excluded	Study design - CA
Szabo S, Audhya IF, Griffin E, Crabtree M, Patel S, Bever A, Iannaccone ST, Gooch KL. 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). Value in Health. 2023 Dec 1;26(12):S486.	Excluded	Study design - CA
Audhya IF, Szabo S, Bever AE, Malone DC, Feeny D, Neumann PI, Bolatova T, Iannaccone ST, Gooch KL. PCR176 time trade-off utility values for health states characterizing progressive muscular	Excluded	Outcome of interest

Reference	Inclusion in Model	Reason for exclusion
degeneration in Duchenne muscular dystrophy (DMD). Value in Health. 2022 Jul 1;25(7):S574.		
Audhya I, Rogula B, Szabo SM, Feeny D, Bolatova T, Gooch K. Exploring the relationship between north star ambulatory assessment and health utilities Index scores in Duchenne muscular dystrophy. Health and Quality of Life Outcomes. 2023 Jul 19;21(1):76	Excluded	Outcome of interest
Morgan G, Brighton S, Samsonroy A, Carlton J, Baranello G, Ung B, Willock R, Iff J. PCR65 Assessment of the EQ-5D and DMD-QoL for Duchenne Muscular Dystrophy: A Patient and Caregiver Study. Value in Health. 2023 Dec 1;26(12):S461.	Excluded	Outcome of interest
Xu RH, Dai Y, Ng SS, Tsang HW, Zhang S, Dong D. Assessing validity of the EQ-5D-5L proxy in children and adolescents with Duchenne muscular dystrophy or spinal muscular atrophy. The European Journal of Health Economics. 2024 Feb;25(1):103-15.	Excluded	Location - outside Europe
Do LA, Sedita LE, Klimchak AC, Salazar R, Kim DD. Cataloging health state utility estimates for Duchenne muscular dystrophy and related conditions. Health and Quality of Life Outcomes. 2024 Sep 2;22(1):72.	Excluded	Outcome of interest
Gallop K, Foerster D, Lawrence C, Denjean E, Van Der Wild J, Acaster S. PMS61 Estimation of Health Utilities for NON-Ambulatory Duchenne Muscular Dystrophy (DMD) Patients and Their Caregivers. Value in Health. 2020 Dec 1;23:S602	Excluded	Outcome of interest
Crossnohere NL, Fischer R, Lloyd A, Prosser LA, Bridges JF. Assessing the appropriateness of the EQ-5D for Duchenne muscular dystrophy: a patient-centered study. Medical Decision Making. 2021 Feb;41(2):209-21.	Included	NA
Crossnohere N, Fischer R, Bridges J. PRO86 health state utility values for stages of functional decline in Duchenne muscular dystrophy: an international study. Value in Health. 2020 May 1;23:S344.	Excluded	Outcome of interest
Schwartz CE, Stark RB, Cella D, Borowiec K, Gooch KL, Audhya IF. Measuring Duchenne muscular dystrophy impact: development of a proxy-reported measure derived from PROMIS item banks. Orphanet journal of rare diseases. 2021 Nov 22;16(1):487.	Excluded	Outcome of interest
Landfeldt E, Lindberg C, Sejersen T. Improvements in health status and utility associated with ataluren for the treatment of nonsense mutation Duchenne muscular dystrophy. Muscle & Nerve. 2020 Mar;61(3):363-8.	Excluded	Outcome of interest
Andreozzi V, Labisa P, Mota M, Monteiro S, Alves R, Almeida J, Vandewalle B, Felix J, Buesch K, Canhão H, Beitia Ortiz de Zarate I. Quality of life and informal care burden associated with duchenne muscular dystrophy in Portugal: the COIDUCH study. Health and quality of life outcomes. 2022 Mar 3;20(1):36.	Excluded	Outcome of interest
Thongsing A, Likasitwattanakul S, Sanmaneechai O. Reliability and validity of the Thai version of the Pediatric Quality of Life inventory™ 3.0 Duchenne Muscular Dystrophy module in Thai children with Duchenne Muscular Dystrophy. Health and quality of life outcomes. 2019 May 2;17(1):76.	Excluded	Outcome of interest
Shehata Z, Metry A, Rabea H, El Sherif R, Abdelrahim M, Dawoud D. Early cost-utility analysis of ataluren and eteplirsen in the treatment of duchenne muscular dystrophy in egypt. Value in Health Regional Issues. 2023 Nov 1;38:109-17.	Excluded	Outcome of interest
Landfeldt E, Mayhew A, Eagle M, Lindgren P, Bell CF, Guglieri M, Straub V, Lochmüller H, Bushby K. Development and psychometric analysis of the Duchenne muscular dystrophy Functional Ability Self-Assessment Tool (DMDSAT). Neuromuscular Disorders. 2015 Dec 1;25(12):937-44.	Excluded	Data duplicacy
Shimizu-Motohashi Y, Merla V, Nagano M, Shima D, Posner N, Evans J. EE472 The Burden-of-Illness of Duchenne Muscular Dystrophy in Japan: A Socioeconomic Survey. Value in Health. 2024 Dec 1;27(12):S148.	Excluded	Study design - CA

Reference	Inclusion in Model	Reason for exclusion
Audhya IF, Szabo SM, Bever A, O'Sullivan F, Malone DC, Feeny D, Neumann P, Iannaccone ST, Jayasinghe P, Gooch KL. Estimating health state utilities in Duchenne muscular dystrophy using the health utilities index and EQ-5D-5L. Journal of Patient-Reported Outcomes. 2023 Dec 15;7(1):132.	Excluded	Location - Outside Europe
Rowen D, Powell P, Mukuria C, Carlton J, Norman R, Brazier J. Deriving a preference-based measure for people with Duchenne muscular dystrophy from the DMD-QoL. Value in Health. 2021 Oct 1;24(10):1499-510.	Excluded	No fit to model health states
Landfeldt E, Lindberg C, Sejersen T. Improvements in health status and utility associated with ataluren for the treatment of nonsense mutation Duchenne muscular dystrophy. Muscle & Nerve. 2020 Mar;61(3):363-8.	Excluded	Outcome of interest
Castro D, Evans J, Jones C, Willock R, Wu Y, Reuben E, Hofmeister S, Vinci I, Hale J, Selby V, Schrader R. EE92 Introduction to the Duchenne Muscular Dystrophy Burden-of-Illness Study Expanded (US AND SPAIN). Value in Health. 2023 Dec 1;26(12):S68.	Excluded	Study design - CA
Cavazza M, Kodra Y, Armeni P, De Santis M, López-Bastida J, Linertová R, Oliva-Moreno J, Serrano-Aguilar P, Posada-de-la-Paz M, Taruscio D, Schieppati A. Social/economic costs and health-related quality of life in patients with Duchenne muscular dystrophy in Europe. The European Journal of Health Economics. 2016 Apr;17(Suppl 1):19-29.	Excluded	No fit to model health states
Landfeldt E, Lindgren P, Bell CF, Guglieri M, Straub V, Lochmüller H, Bushby K. Quantifying the burden of caregiving in Duchenne muscular dystrophy. Journal of neurology. 2016 May;263(5):906-15.	Included	NA
Mendell JR, Muntoni F, McDonald CM, Mercuri EM, Ciafaloni E, Komaki H, Leon-Astudillo C, Nascimento A, Proud C, Schara-Schmidt U, Veerapandiyan A. AAV gene therapy for Duchenne muscular dystrophy: the EMBARK phase 3 randomized trial. Nature medicine. 2025 Jan;31(1):332-41.	Excluded	Outcome of interest
Landfeldt E, Zhang R, Buesch K. MSR21 Cost-Effectiveness Analysis of Treatments for Nonsense Mutation Duchenne Muscular Dystrophy: Expert Validation of Model Face Validity. Value in Health. 2022 Jul 1;25(7):S521-2.	Excluded	Outcome of interest
Magnetta DA, Kang J, Wearden PD, Smith KJ, Feingold B. Cost-effectiveness of ventricular assist device destination therapy for advanced heart failure in Duchenne muscular dystrophy. Pediatric cardiology. 2018 Aug;39(6):1242-8.	Excluded	Outcome of interest
Alemdaroglu-Gürbüz I, Bulut N, Bozgeyik S, Ulug N, Arslan SS, Yilmaz Ö, Karaduman A. Reliability and validity of the turkish translation of pedsql™ multidimensional Fatigue scale in Duchenne Muscular Dystrophy. Neurosciences journal. 2019 Oct 1;24(4):302-10.	Excluded	Outcome of interest
Bello L, Deroo V, Arrabal N, Wright EJ. PCR114 modelling the benefit of givinostat on Duchenne muscular dystrophy (DMD) patients, and their caregivers. Value in Health. 2024 Dec 1;27(12):S527-8.	Excluded	Outcome of interest
Landfeldt E, Zhang R, Childs AM, Johannsen J, O'Rourke D, Sejersen T, Strautmanis J, Schara-Schmidt U, Tulinius M, Walter MC, Willis T. Assessment of face validity of a disease model of nonsense mutation Duchenne muscular dystrophy: a multi-national Delphi panel study. Journal of Medical Economics. 2022 Dec 31;25(1):808-16.	Excluded	Outcome of interest
De Waele L, Cremers J, Debien E, Gielis E, Maenen V, Vanoppen I, Van Stappen T, Beeckman L, Posner N, Dukacz S, Jiang L. 336P Quantifying the burden-of-illness of Duchenne muscular dystrophy in Belgium: an interim analysis of a site-based survey. Neuromuscular Disorders. 2024 Oct 1;43:104441-667.	Excluded	Study design - CA

Reference	Inclusion in Model	Reason for exclusion
Landfeldt E, Mayhew A, Straub V, Lochmüller H, Bushby K, Lindgren P. Psychometric analysis of the pediatric quality of life inventory 3.0 neuromuscular module administered to patients with duchenne muscular dystrophy: a rasch analysis. Muscle & nerve. 2018 Sep;58(3):367-73	Excluded	Outcome of interest
Chieffo DP, Moriconi F, Pane M, Lucibello S, Ferraroli E, Norcia G, Ricci M, Capasso A, Cicala G, Buchignani B, Coratti G. A longitudinal follow-up study of intellectual function in duchenne muscular dystrophy over age: is it really stable?. Journal of Clinical Medicine. 2023 Jan 4;12(2):403.	Excluded	Outcome of interest
Audhya IF, Patel S, Yang M, Tuttle E, Martins B, Yang F, Lan JJ, Gooch KL. PCR284 Real-DMD: Caregiver Baseline Characteristics From an Electronic Survey of Long-Term Real-World Experiences of Patients With Duchenne Muscular Dystrophy (DMD). Value in Health. 2024 Dec 1;27(12):S563.	Excluded	Outcome of interest
Patel S, Yang M, Tuttle E, Martins B, Yang F, Gooch KL, Audhya IF. PCR44 Real-DMD: Baseline Findings From an Electronic Observer-Reported Outcome (OBSRO) Survey of Long-Term Real-World Experiences of Patients with Duchenne Muscular Dystrophy (DMD). Value in Health. 2024 Jun 1;27(6):S304.	Excluded	Outcome of interest
Landfeldt E, Alfredsson L, Straub V, Lochmüller H, Bushby K, Lindgren P. Economic evaluation in Duchenne muscular dystrophy: model frameworks for cost-effectiveness analysis. Pharmacoeconomics. 2017 Feb;35(2):249-58.	Included	NA
Ishizaki M, Kobayashi M, Hashimoto H, Nakamura A, Maeda Y, Ueyama H, Matsumura T. Caregiver burden with Duchenne and Becker muscular dystrophy in Japan: a clinical observation study. Internal Medicine. 2024 Feb 1;63(3):365-72.	Excluded	Outcome of interest
Verhaart I, Hofmeister S, Franken-Verbeek M, Vroom E, Mariakaki A, Furlong P. EP. 79The impact of ventilation on non-ambulatory patients with DMD. Neuromuscular Disorders. 2019 Oct 1;29:S175.	Excluded	Outcome of interest
Roni P, Sarah B, Shannon W, Clarissa E, Aileen D, Laura M, Nancy, Unni N. Measuring priorities and goals of children with duchnne muscular dystrophy to develop a meaningful patient reported outcome measure. 2016	Excluded	Outcome of interest
Campbell C, McColl E, McDermott MP, Martens WB, Guglieri M, Griggs RC, Straub V, Childs AM, Ciafaloni E, Shieh PB, Spinty S. Health related quality of life in young, steroid-naïve boys with Duchenne muscular dystrophy. Neuromuscular Disorders. 2021 Nov 1;31(11):1161-8	Excluded	Outcome of interest
Jesus A, Bennett C, Masterson C, Brenner L, Scharf R. Self-and Caregiver-Reported Participation, Quality of Life, and Related Mood and Behavior Challenges in People Living With Dystrophinopathies. Pediatric Neurology. 2024 Feb 1;151:37-44.	Excluded	Outcome of interest
Klimchak AC, Sedita LE, Rodino-Klapac LR, Mendell JR, McDonald CM, Gooch KL, Malone DC. Assessing the value of delandistrogene moxeparvovec (SRP-9001) gene therapy in patients with Duchenne muscular dystrophy in the United States. Journal of Market Access & Health Policy. 2023 Dec 31;11(1):2216518.	Excluded	Outcome of interest
Schwartz CE, Stark RB, Borowiec K, Audhya IF, Gooch KL. Interplay of disability, caregiver impact, and out-of-pocket expenditures in Duchenne muscular dystrophy: a cohort study. Journal of Patient-Reported Outcomes. 2022 Mar 10;6(1):21.	Excluded	Outcome of interest
NICE-TA1031. Vamorolone for treating Duchenne muscular dystrophy in people 4 years and over. https://www.nice.org.uk/guidance/ta1031	Excluded	Outcome of interest

CA: Conference abstract

Quality assessment and generalizability of estimates

N/A

Unpublished data

N/A.

Appendix J. Literature searches for input to the health economic model

External literature for input to the health economic model

The aim of this SLR was to identify and gather cost-effectiveness evidence and costs and resource use associated with the management treatment of patients with DMD and their caregivers.

As detailed in Table 88, Table 89, and Table 90 the original economic (economic evaluations and healthcare cost and resource use (HCRU) SLR search was conducted in 2017, followed by an update in 2019, 2023 and 2025. The searches were performed in the following indexed databases:

- Embase® (using Embase.com)
- MEDLINE®; MEDLINE In-Process (using PubMed.com)
- The Cochrane Library, including the following:
    - Cochrane Central Register of Controlled Trials (CENTRAL)

Table 88 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	https://www.embase.com/	Original SLR: Inception–2017 SLR updates: 2019, 2023 and 2025	Current SLR update: 10.03.2025
Medline	https://pubmed.ncbi.nlm.nih.gov/	Original SLR: Inception–2017 SLR updates: 2019, 2023 and 2025	Current SLR update: 10.03.2025
CENTRAL	https://www.cochranelibrary.com/advanced-search	Original SLR: Inception–2017 SLR updates: 2019, 2023 and 2025	Current SLR update: 10.03.2025

Abbreviations: CENTRAL = Cochrane Central Register of Controlled Trials, Embase = Excerpta Medica Database, MEDLINE = Medical Literature Analysis and Retrieval System Online, SLR = Systematic literature review.

Table 89 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
NICE	www.nice.org.uk		12.03.2025
SMC	https://scottishmedicines.org.uk/		12.03.2025

Abbreviations: NICE = National Institute for Health and Care Excellence, SMC = Scottish Medicines Consortium.

Table 90 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
Muscular Dystrophy Association Scientific Conference	https://www.mdaconference.org/	Manual search	duchenne muscular dystrophy	19.03.2025
International Annual Congress of the World Muscle Society	https://www.worldmusclesociety.org/page/past-world-muscle-society-congresses	Manual search	duchenne muscular dystrophy	17.03.2025

Search strategies

The SLR was conducted based on PRISMA, Table 94 (Economic evaluations) and Table 95 (healthcare cost and resource use) and generated from the research question pertinent to each selection.

The study selection process was performed by two independent reviewers based on a two-step approach: i) Abstracts/titles screening; ii) In-depth review of full-text articles.

First, titles and abstracts were screened by two independent reviewers for relevancy based on a predefined set of eligibility criteria (Table 94 and Table 95). Any discrepancy in study selection was resolved by consensus or with the help of a third reviewer. Relevant full-text citations were retrieved after abstract and title screening. Two reviewers independently assessed study eligibility, documenting exclusion reasons and discrepancies were resolved by a third reviewer.

After the records were identified and collected based on the search strategy, the references for all included records were stored in EndNote. The meta data and outcome data were collected and collated in MS Excel grid.

Table 91 Search strategy for Embase® (10thMarch 2025)

No.	Query	Results
Economic evaluation		
#1	'duchenne muscular dystrophy'/syn OR 'duchenne muscular dystrophy' OR 'duchenne muscular dystrophy':ab,ti OR duchenne:ab,ti OR ((duchenne NEAR/3 dystrophy):ab,ti) OR 'duchenne muscular dystrophy'/exp	26525
#2	('decision theory'/exp OR 'pharmacoeconomics'/exp OR 'cost effectiveness analysis'/exp OR 'cost minimization analysis'/exp OR 'economic evaluation'/exp OR 'cost utility analysis'/exp OR 'cost benefit analysis'/exp OR 'quality adjusted life year'/exp OR 'decision tree'/exp OR 'monte carlo method'/exp OR 'hidden markov model'/exp OR 'sensitivity analysis'/exp OR ((cost NEXT/1 estimate*):ab,ti,kw) OR ((cost NEXT/1 variable*):ab,ti,kw) OR ((unit NEXT/1 cost*):ab,ti,kw) OR economic*:ab,ti,kw OR pharmacoeconomic*:ab,ti,kw OR markov*:ab,ti,kw OR ((decision NEXT/2 tree*):ab,ti,kw) OR ((decision NEXT/2 analy*):ab,ti,kw) OR ((monte NEXT/1 carlo):ab,ti,kw) OR (((incremental OR qaly OR 'quality adjusted life years') NEAR/3 cost):ab,ti,kw) OR ((cost NEAR/3 (effect* OR utility* OR benefit OR conseq* OR minimi* OR increment* OR qaly* OR ly* OR 'quality adjusted life year*' OR 'life year*')):ab,ti,kw) OR icer:ab,ti,kw OR qaly:ab,ti,kw OR 'quality adjusted life year*':ab,ti,kw OR 'life year*':ab,ti,kw OR (((markov* OR simulat* OR decisio* OR analy* OR 'area under curve' OR partition* OR survival* OR economic* OR transitio* OR state* OR discrete* OR individual* OR cohort*) NEAR/3 model*):ab,ti,kw) OR 'economic model'/exp OR 'markov chain'/exp OR 'simulation'/exp OR 'budget'/exp) AND [2020-2025]/py	783070
#3	#1 AND #2	495
#4	#1 AND #2 AND ([editorial]/lim OR [letter]/lim OR [note]/lim OR [review]/lim OR [short survey]/lim) AND [animals]/lim	6
#5	#4 NOT #5	489
#6	# 5 AND [2023-2025]/py	250
HCRU		
#1	'duchenne muscular dystrophy'/syn OR 'duchenne muscular dystrophy' OR 'duchenne muscular dystrophy':ab,ti OR duchenne:ab,ti OR ((duchenne NEAR/3 dystrophy):ab,ti) OR 'duchenne muscular dystrophy'/exp	26525
#2	('health economics'/exp OR 'cost control'/exp OR 'health care cost'/exp OR 'drug cost'/exp OR 'hospital cost'/exp OR 'cost of illness'/exp OR 'health care utilization'/exp OR 'resource management'/exp OR 'resource allocation'/exp OR ((healthcare	2537064

	NEXT/1 cost*):ab,ti,kw) OR ((unit NEXT/1 cost*):ab,ti,kw) OR price*:ab,ti,kw OR pricing:ab,ti,kw OR ((resource* NEXT/2 allocat*):ab,ti,kw) OR ((health*care NEXT/1 (utilisation OR utilization)):ab,ti,kw) OR (('health care' NEXT/1 (utilisation OR utilization)):ab,ti,kw) OR ((resource NEXT/1 (utilisation OR utilization OR use)):ab,ti,kw) OR ((cost* NEAR/3 (treat* OR therap*)):ab,ti,kw) OR (((total OR direct OR indirect OR medical OR drug OR administration OR laborat* OR diagnos* OR productivity OR illness) NEAR/2 (cost OR costs)):ab,ti,kw) OR 'hospitalization cost'/exp OR 'length of stay'/exp OR 'economic aspect'/exp OR 'socioeconomics'/exp OR 'financial management'/exp OR 'health care financing'/exp OR 'fee'/exp OR 'budget'/exp OR economic:ab,ti,kw OR economics:ab,ti,kw OR cost:ab,ti,kw OR costs:ab,ti,kw OR 'absenteeism'/exp OR 'presenteeism'/exp OR 'medical leave'/exp OR 'productivity'/exp OR (((sick* OR illness OR disab*) NEAR/3 leave*):ab,ti,kw) OR ((work* NEAR/3 (absence OR absent OR impair* OR disab*)):ab,ti,kw) OR productivity:ab,ti,kw OR ((burden NEAR/2 (disease* OR illness)):ab,ti,kw) OR 'caregiver burden'/exp OR 'caregiver support'/exp OR carer*:ab,ti,kw OR caregiver*:ab,ti,kw OR 'care giver':ab,ti,kw OR 'care-giver':ab,ti,kw OR 'care givers':ab,ti,kw OR 'care-givers':ab,ti,kw) AND [2015-2025]/py	
#3	#1 AND #2	1652
#4	#1 AND #2 AND ([editorial]/lim OR [letter]/lim OR [note]/lim OR [review]/lim OR [short survey]/lim) AND [animals]/lim	13
#5	#4 NOT #5	1639
#6	#5 AND [2023-2025]/py	

Table 92 Search strategy for MEDLINE® (10th March 2025)

No.	Query	Results
Economic evaluation		
#1	duchenne muscular dystrophy[Title/Abstract]	12286
#2	duchenne[Title/Abstract]	15069
#3	duchenne muscular dystrophy[MeSH Terms]	7836
#4	duchenne	16413
#5	"duchenne dystrophy"[Tiab:~3]	13989
#6	#1 OR #2 OR #3 OR #4 OR #5	16413
#7	"decision theory"[MeSH Terms] OR "economics, pharmaceutical"[MeSH Terms] OR "cost effectiveness analysis"[MeSH Terms] OR "costs and cost analysis"[MeSH Terms] OR "cost benefit analysis"[MeSH Terms] OR "cost	1099228

	benefit analysis"[MeSH Terms] OR "cost benefit analysis"[MeSH Terms] OR "quality adjusted life years"[MeSH Terms] OR "decision trees"[MeSH Terms] OR "monte carlo method"[MeSH Terms] OR "hidden markov model"[All Fields] OR "sensitivity analysis"[All Fields] OR ("cost"[Title/Abstract] AND ("NEXT"[All Fields] AND "1 estimate*"[Title/Abstract])) OR ("cost"[Title/Abstract] AND ("NEXT"[All Fields] AND "1 variable*"[Title/Abstract])) OR ("unit"[Title/Abstract] AND ("NEXT"[All Fields] AND "1 cost*"[Title/Abstract])) OR "economic*"[Title/Abstract] OR "pharmacoeconomic*"[Title/Abstract] OR "markov*"[Title/Abstract] OR ("decision"[Title/Abstract] AND ("NEXT"[All Fields] AND "2 tree*"[Title/Abstract])) OR ("decision"[Title/Abstract] AND ("NEXT"[All Fields] AND "2 analy*"[Title/Abstract])) OR ("monte"[Title/Abstract] AND ("next 1"[All Fields] AND "carlo"[Title/Abstract])) OR (("incremental"[Title/Abstract] OR "QALY"[Title/Abstract] OR "quality adjusted life years"[Title/Abstract]) AND ("NEAR"[All Fields] AND "3 cost"[Title/Abstract])) OR (("cost"[Title/Abstract] AND "near 3"[All Fields]) AND ("effect*"[Title/Abstract] OR "utility*"[Title/Abstract] OR "benefit"[Title/Abstract] OR "conseq*"[Title/Abstract] OR "minimi*"[Title/Abstract] OR "increment*"[Title/Abstract] OR "qaly*"[Title/Abstract] OR "quality adjusted life year*"[Title/Abstract] OR "life year*"[Title/Abstract])) OR "ICER"[Title/Abstract] OR "QALY"[Title/Abstract] OR "quality adjusted life year*"[Title/Abstract] OR "life year*"[Title/Abstract] OR (("markov*"[Title/Abstract] OR "simulat*"[Title/Abstract] OR "decisio*"[Title/Abstract] OR "analy*"[Title/Abstract] OR "area under curve"[Title/Abstract] OR "partition*"[Title/Abstract] OR "survival*"[Title/Abstract] OR "economic*"[Title/Abstract] OR "transitio*"[Title/Abstract] OR "state*"[Title/Abstract] OR "discrete*"[Title/Abstract] OR "individual*"[Title/Abstract] OR "cohort*"[Title/Abstract]) AND ("NEAR"[All Fields] AND "3 model*"[Title/Abstract])) OR "models, economic"[MeSH Terms] OR "markov chains"[MeSH Terms] OR "computer simulation"[MeSH Terms] OR "budgets"[MeSH Terms]	
#8	("decision theory"[MeSH Terms] OR "economics, pharmaceutical"[MeSH Terms] OR "cost effectiveness analysis"[MeSH Terms] OR "costs and cost analysis"[MeSH Terms] OR "cost benefit analysis"[MeSH Terms] OR "cost benefit analysis"[MeSH Terms] OR "cost benefit analysis"[MeSH Terms] OR "quality adjusted life years"[MeSH Terms] OR "decision trees"[MeSH Terms] OR "monte carlo method"[MeSH Terms] OR "hidden markov model"[All Fields] OR "sensitivity analysis"[All Fields] OR ("cost"[Title/Abstract] AND ("NEXT"[All Fields] AND "1 estimate*"[Title/Abstract])) OR ("cost"[Title/Abstract] AND ("NEXT"[All Fields] AND "1 variable*"[Title/Abstract])) OR ("unit"[Title/Abstract] AND ("NEXT"[All Fields] AND "1 cost*"[Title/Abstract])) OR "economic*"[Title/Abstract] OR "pharmacoeconomic*"[Title/Abstract] OR "markov*"[Title/Abstract] OR ("decision"[Title/Abstract] AND ("NEXT"[All Fields] AND "2 tree*"[Title/Abstract])) OR ("decision"[Title/Abstract] AND ("NEXT"[All Fields] AND "2 analy*"[Title/Abstract])) OR ("monte"[Title/Abstract] AND ("next 1"[All Fields] AND "carlo"[Title/Abstract])) OR (("incremental"[Title/Abstract] OR "QALY"[Title/Abstract] OR "quality adjusted life years"[Title/Abstract]) AND ("NEAR"[All Fields] AND "3 cost"[Title/Abstract])) OR (("cost"[Title/Abstract] AND "near 3"[All Fields]) AND	320401

	("effect*"[Title/Abstract] OR "utility*"[Title/Abstract] OR "benefit"[Title/Abstract] OR "conseq*"[Title/Abstract] OR "minimi*"[Title/Abstract] OR "increment*"[Title/Abstract] OR "qaly*"[Title/Abstract] OR "quality adjusted life year*"[Title/Abstract] OR "life year*"[Title/Abstract])) OR "ICER"[Title/Abstract] OR "QALY"[Title/Abstract] OR "quality adjusted life year*"[Title/Abstract] OR "life year*"[Title/Abstract] OR (("markov*"[Title/Abstract] OR "simulat*"[Title/Abstract] OR "decisio*"[Title/Abstract] OR "analy*"[Title/Abstract] OR "area under curve"[Title/Abstract] OR "partition*"[Title/Abstract] OR "survival*"[Title/Abstract] OR "economic*"[Title/Abstract] OR "transitio*"[Title/Abstract] OR "state*"[Title/Abstract] OR "discrete*"[Title/Abstract] OR "individual*"[Title/Abstract] OR "cohort*"[Title/Abstract]) AND ("NEAR"[All Fields] AND "3 model*"[Title/Abstract])) OR "models, economic"[MeSH Terms] OR "markov chains"[MeSH Terms] OR "computer simulation"[MeSH Terms] OR "budgets"[MeSH Terms]) AND (2020:2025[pdat])	
#9	#6 AND #8	62
#10	#6 AND #8 AND (animal[Filter])	10
#11	#9 NOT #10	52
#12	#12 AND (2023:2025[pdat])	30
HCRU		
#1	duchenne muscular dystrophy[Title/Abstract]	12286
#2	duchenne[Title/Abstract]	15069
#3	duchenne muscular dystrophy[MeSH Terms]	7836
#4	duchenne	16413
#5	"duchenne dystrophy"[Tiab:~3]	13989
#6	#1 OR #2 OR #3 OR #4 OR #5	16413
#7	(("health care economics and organizations"[MeSH Terms] OR "cost control"[MeSH Terms] OR "health care costs"[MeSH Terms] OR "drug costs"[MeSH Terms] OR "hospital costs"[MeSH Terms] OR "cost of illness"[MeSH Terms] OR "healthcare utilization"[All Fields] OR (("health resources"[MeSH Terms] OR ("health"[All Fields] AND "resources"[All Fields]) OR "health resources"[All Fields] OR "resource"[All Fields] OR "resources"[All Fields] OR "resource s"[All Fields] OR "resourced"[All Fields] OR "resourceful"[All Fields] OR "resourcefulness"[All Fields] OR "resourcing"[All Fields]) AND ("organization and administration"[MeSH Terms] OR "disease management"[MeSH Terms])) OR "resource allocation"[MeSH Terms] OR ("healthcare"[Title/Abstract] AND ("NEAR"[All Fields] AND "1 cost*"[Title/Abstract])) OR ("unit"[Title/Abstract] AND ("NEAR"[All Fields] AND "1	237620

	cost*"[Title/Abstract])) OR "price*"[Title/Abstract] OR "pricing"[Title/Abstract] OR ("resource*"[Title/Abstract] AND ("NEAR"[All Fields] AND "2 allocat*"[Title/Abstract])) OR (("health*care"[Title/Abstract] AND "near 1"[All Fields]) AND ("utilisation"[Title/Abstract] OR ("utili"[All Fields] AND "ation"[Title/Abstract]))) OR (("health*care"[Title/Abstract] AND "near 1"[All Fields]) AND ("utilisation"[Title/Abstract] OR ("utili"[All Fields] AND "ation"[Title/Abstract]))) OR (("resource"[Title/Abstract] AND "near 1"[All Fields]) AND ("utilisation"[Title/Abstract] OR "utilization"[Title/Abstract] OR "use"[Title/Abstract])) OR (("cost*"[Title/Abstract] AND "near 3"[All Fields]) AND ("treat*"[Title/Abstract] OR "therap*"[Title/Abstract])) OR ((("total"[Title/Abstract] OR "direct"[Title/Abstract] OR "indirect"[Title/Abstract] OR "medical"[Title/Abstract] OR "drug"[Title/Abstract] OR "administration"[Title/Abstract] OR "laborat*"[Title/Abstract] OR "diagnos*"[Title/Abstract] OR "productivity"[Title/Abstract] OR "illness"[Title/Abstract]) AND "near 2"[All Fields]) AND ("cost"[Title/Abstract] OR "costs"[Title/Abstract])) OR (("hospital s"[All Fields] OR "hospitalisation"[All Fields] OR "hospitalization"[MeSH Terms] OR "hospitalization"[All Fields] OR "hospitalised"[All Fields] OR "hospitalising"[All Fields] OR "hospitality"[All Fields] OR "hospitalisations"[All Fields] OR "hospitalizations"[All Fields] OR "hospitalize"[All Fields] OR "hospitalized"[All Fields] OR "hospitalizing"[All Fields] OR "hospitals"[MeSH Terms] OR "hospitals"[All Fields] OR "hospital"[All Fields]) AND "costs and cost analysis"[MeSH Terms]) OR "length of stay"[MeSH Terms] OR "economic aspect"[All Fields] OR "socioeconomic factors"[MeSH Terms] OR "financial management"[MeSH Terms] OR (("delivery of health care"[MeSH Terms] OR ("delivery"[All Fields] AND "health"[All Fields] AND "care"[All Fields]) OR "delivery of health care"[All Fields] OR ("health"[All Fields] AND "care"[All Fields]) OR "health*care"[All Fields]) AND "economics"[MeSH Terms]) OR "fee"[All Fields] OR "budgets"[MeSH Terms] OR "economic"[Title/Abstract] OR "economics"[Title/Abstract] OR "cost"[Title/Abstract] OR "costs"[Title/Abstract] OR "absenteeism"[MeSH Terms] OR "presenteeism"[MeSH Terms] OR "medical leave"[All Fields] OR "efficiency"[MeSH Terms] OR ("sick*"[Title/Abstract] OR "illness"[Title/Abstract] OR "disab*"[Title/Abstract])) AND ("NEAR"[All Fields] AND "3 leave*"[Title/Abstract])) OR (("work*"[Title/Abstract] AND "near 3"[All Fields]) AND ("absence"[Title/Abstract] OR "absent"[Title/Abstract] OR "impair*"[Title/Abstract] OR "disab*"[Title/Abstract])) OR "productivity"[Title/Abstract] OR (("burden"[Title/Abstract] AND "near 2"[All Fields]) AND ("disease*"[Title/Abstract] OR "illness"[Title/Abstract])) OR "caregiver burden"[MeSH Terms] OR "caregiver support"[All Fields] OR "carer*"[Title/Abstract] OR "caregiver*"[Title/Abstract] OR "caregiver"[Title/Abstract] OR "care-giver"[Title/Abstract] OR ("caregivers"[MeSH Terms] OR "caregivers"[All Fields] OR ("care"[All Fields] AND "givers"[All Fields]) OR "care givers"[All Fields])	
#8	((("health care economics and organizations"[MeSH Terms] OR "cost control"[MeSH Terms] OR "health care costs"[MeSH Terms] OR "drug costs"[MeSH Terms] OR "hospital costs"[MeSH Terms] OR "cost of illness"[MeSH Terms] OR "healthcare utilization"[All Fields] OR (("health resources"[MeSH Terms] OR ("health"[All Fields] AND "resources"[All Fields]) OR "health resources"[All Fields] OR "resource"[All Fields] OR	151078

"resources"[All Fields] OR "resource s"[All Fields] OR "resourced"[All Fields] OR "resourceful"[All Fields] OR "resourcefulness"[All Fields] OR "resourcing"[All Fields]) AND ("organization and administration"[MeSH Terms] OR "disease management"[MeSH Terms])) OR "resource allocation"[MeSH Terms] OR ("healthcare"[Title/Abstract] AND ("NEAR"[All Fields] AND "1 cost*"[Title/Abstract])) OR ("unit"[Title/Abstract] AND ("NEAR"[All Fields] AND "1 cost*"[Title/Abstract])) OR "price*"[Title/Abstract] OR "pricing"[Title/Abstract] OR ("resource*"[Title/Abstract] AND ("NEAR"[All Fields] AND "2 allocat*"[Title/Abstract])) OR (("health*care"[Title/Abstract] AND "near 1"[All Fields]) AND ("utilisation"[Title/Abstract] OR ("utili"[All Fields] AND "ation"[Title/Abstract]))) OR (("health*care"[Title/Abstract] AND "near 1"[All Fields]) AND ("utilisation"[Title/Abstract] OR ("utili"[All Fields] AND "ation"[Title/Abstract]))) OR (("resource"[Title/Abstract] AND "near 1"[All Fields]) AND ("utilisation"[Title/Abstract] OR "utilization"[Title/Abstract] OR "use"[Title/Abstract])) OR (("cost*"[Title/Abstract] AND "near 3"[All Fields]) AND ("treat*"[Title/Abstract] OR "therap*"[Title/Abstract])) OR ((("total"[Title/Abstract] OR "direct"[Title/Abstract] OR "indirect"[Title/Abstract] OR "medical"[Title/Abstract] OR "drug"[Title/Abstract] OR "administration"[Title/Abstract] OR "laborat*"[Title/Abstract] OR "diagnos*"[Title/Abstract] OR "productivity"[Title/Abstract] OR "illness"[Title/Abstract]) AND "near 2"[All Fields]) AND ("cost"[Title/Abstract] OR "costs"[Title/Abstract])) OR (("hospital s"[All Fields] OR "hospitalisation"[All Fields] OR "hospitalization"[MeSH Terms] OR "hospitalization"[All Fields] OR "hospitalised"[All Fields] OR "hospitalising"[All Fields] OR "hospitality"[All Fields] OR "hospitalisations"[All Fields] OR "hospitalizations"[All Fields] OR "hospitalize"[All Fields] OR "hospitalized"[All Fields] OR "hospitalizing"[All Fields] OR "hospitals"[MeSH Terms] OR "hospitals"[All Fields] OR "hospital"[All Fields]) AND "costs and cost analysis"[MeSH Terms]) OR "length of stay"[MeSH Terms] OR "economic aspect"[All Fields] OR "socioeconomic factors"[MeSH Terms] OR "financial management"[MeSH Terms] OR (("delivery of health care"[MeSH Terms] OR ("delivery"[All Fields] AND "health"[All Fields] AND "care"[All Fields]) OR "delivery of health care"[All Fields] OR ("health"[All Fields] AND "care"[All Fields]) OR "health*care"[All Fields]) AND "economics"[MeSH Terms]) OR "fee"[All Fields] OR "budgets"[MeSH Terms] OR "economic"[Title/Abstract] OR "economics"[Title/Abstract] OR "cost"[Title/Abstract] OR "costs"[Title/Abstract] OR "absenteeism"[MeSH Terms] OR "presenteeism"[MeSH Terms] OR "medical leave"[All Fields] OR "efficiency"[MeSH Terms] OR ("sick*"[Title/Abstract] OR "illness"[Title/Abstract] OR "disab*"[Title/Abstract])) AND ("NEAR"[All Fields] AND "3 leave*"[Title/Abstract])) OR (("work*"[Title/Abstract] AND "near 3"[All Fields]) AND ("absence"[Title/Abstract] OR "absent"[Title/Abstract] OR "impair*"[Title/Abstract] OR "disab*"[Title/Abstract])) OR "productivity"[Title/Abstract] OR (("burden"[Title/Abstract] AND "near 2"[All Fields]) AND ("disease*"[Title/Abstract] OR "illness"[Title/Abstract])) OR "caregiver burden"[MeSH Terms] OR "caregiver support"[All Fields] OR "carer*"[Title/Abstract] OR "caregiver*"[Title/Abstract] OR "caregiver"[Title/Abstract] OR "care-giver"[Title/Abstract] OR ("caregivers"[MeSH Terms] OR "caregivers"[All Fields] OR ("care"[All

	Fields] AND "givers"[All Fields]) OR "care givers"[All Fields])) AND (2015:2025[pdat])	
#9	#6 AND #8	189
#10	#6 AND #8 AND (animal[Filter])	5
#11	#9 NOT #10	184
#12	#11 AND (2023:2025[pdat])	59

Table 93 Search strategy for Cochrane library (10th March 2025)

No.	Query	Results
#1	Muscular Dystrophy, Duchenne	991
#2	(duchenne muscular dystrophy or duchenne):ti,ab,kw	992
#3	duchenne near/3 dystrophy	984
#4	Vamorolone OR idebenone OR ataluren OR steroids	13959
#5	#1 or #2 or #3	1020
#6	#4 and #5	187
#7	Time filter: 2023-2025	16

Inclusion and exclusion criteria used for assessment of studies for Economic Evaluation are presented in Table 94.

Table 94 Inclusion and exclusion criteria used for assessment of studies (Economic evaluations)

	Inclusion criteria	Exclusion criteria
Population	• Patients with DMD	• Studies that include any other patients/populations
Intervention/comparators	• Any intervention for the treatment of DMD	• None
Outcomes	• Cost per QALY gained • Cost per life-year gained • ICERs	• No reported outcomes of interest
Study type	• Economic evaluations:	• Burden of disease study • Resource use study

	Inclusion criteria	Exclusion criteria
	▪ Cost-effectiveness analysis ▪ Cost-utility analysis ▪ Cost-benefit analysis ▪ Cost-minimisation analysis • Economic evaluation alongside clinical trials (EEACT)	• Budget impact study
Publication type	• Article, conference abstract, conference paper, article in press	• Short survey • Reviews • Letters • Comment articles • Systematic literature reviews*
Language restrictions	• English	• Non-English
Date	• No restrictions	NA

*SLRs will be checked for any additional relevant studies.

Abbreviations: DMD – Duchenne Muscular Dystrophy; EEACT – Economic evaluation alongside clinical trials; QALY – Quality-adjusted life-year; SLR – Systematic literature review

Inclusion and exclusion criteria used for assessment of studies for Healthcare cost and resource use are presented in Table 95.

Table 95 Inclusion and exclusion criteria used for assessment of studies (Healthcare Cost and Resource use)

	Inclusion criteria	Exclusion criteria
Population	• Patients with DMD • Carers of patients with DMD	• Studies that include any other patients/populations
Intervention/comparators	• Any intervention for DMD	• None
Outcomes	• Unit costs (e.g. drug, monitoring, administration, adverse event) • Resource use (e.g. number of hospital days, number of A&E admissions,	• No reported outcomes of interest

	Inclusion criteria	Exclusion criteria
	number of caregiver days) • Cost per QALY gained* • Cost per life-year gained* • Budget impact • Cost of illness	
Study type	• Cost study • Burden of disease study • Resource use study • Economic evaluations: ▪ Cost-effectiveness analysis ▪ Cost-utility analysis ▪ Cost-benefit analysis ▪ Cost-minimisation analysis • WTP studies • Economic evaluation alongside clinical trials (EEACT)	• Individual case study reports
Publication type	• Article, conference abstract, conference paper, article in press	• Short survey • Reviews • Letters • Comment articles • Systematic literature reviews*
Language restrictions	• English	• Non-English
Date	• No restriction	NA

* Studies reporting QALYs/LYs might include data points for cost or/and resource use outcomes and thus will be included for full text screening to verify relevant outcomes

**SLRs will be checked for any additional relevant studies.

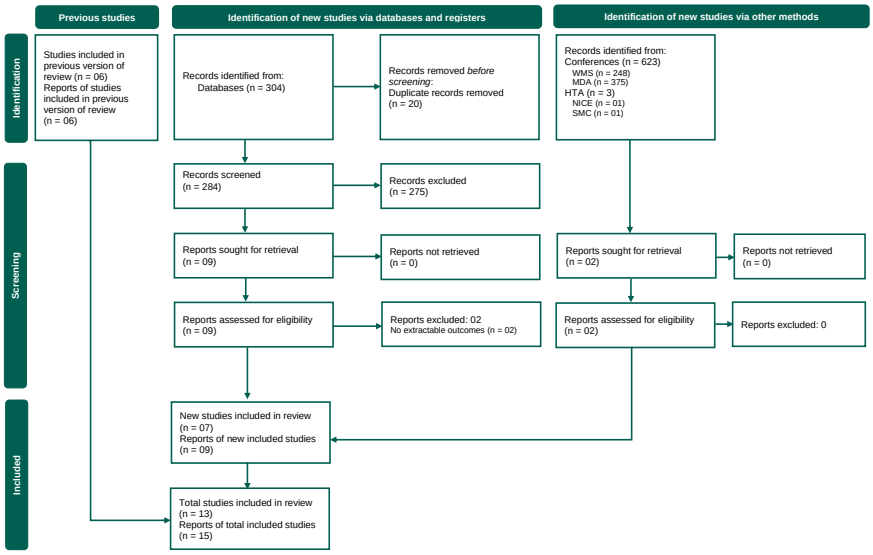
Abbreviations: DMD – Duchenne Muscular Dystrophy; EEACT – Economic evaluation alongside clinical trials; QALY – Quality-adjusted life-year; SLR – Systematic literature review; WTP – Willingness to pay

The PRISMA flow diagram of the economic SLR for Economic evaluations is presented in Figure 24. The current SLR update identified a total of 304 records from three biomedical databases—Embase, MEDLINE, and Cochrane—using the search strategies outlined in Table 91, Table 92, and Table 93 (Economic evaluation). Deduplication resulted in 284

titles/abstracts being screened by two independent reviewers. Title and abstract screening led to inclusion of nine publications which were thoroughly reviewed by two independent reviewers using full-text articles to confirm their inclusion. Of these, seven were included based on the pre-defined PICOS criteria (see Table 94). Grey literature from relevant conferences, NICE and SMC, and bibliographic search within relevant SLRs led to the inclusion of two records. Therefore, a total of nine records were included for seven unique studies in the SLR update.

Based on the previous SLR conducted in 2017 followed by SLR updates conducted in 2017, 2019 and 2023 along with the current SLR update, a total of 15 reports were included in the review. Of these, 13 unique studies were identified.

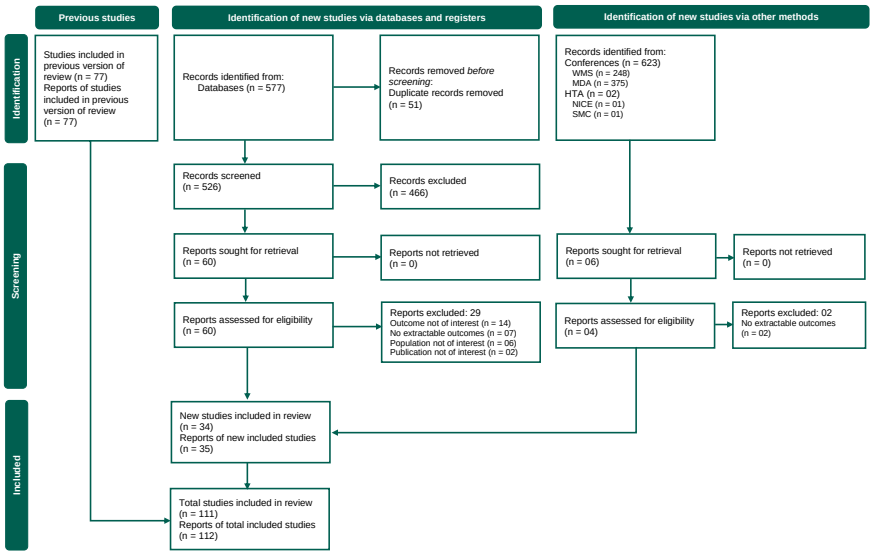
Figure 24 PRISMA flow diagram for economic evaluations update



The PRISMA flow diagram of the economic SLR for Economic evaluations is presented in Figure 25. The current SLR update identified a total of 577 records from three biomedical databases—Embase, MEDLINE, and Cochrane—using the search strategies outlined in Table 91, Table 92, and Table 93 (HCRU). Deduplication resulted in 526 titles/abstracts being screened by two independent reviewers. Title and abstract screening led to the inclusion of 60 publications which were thoroughly reviewed by two independent reviewers using full-text articles to confirm their inclusion. Of these, 31 were included based on the pre-defined PICOS criteria (see Table 95). Grey literature from relevant conferences, NICE and SMC, and bibliographic search within relevant SLRs led to the inclusion of four records. Therefore, a total of 35 records were included for 34 unique studies in the SLR update.

Based on the previous SLR conducted in 2017 followed by SLR updates conducted in 2017, 2019 and 2023 along with the current SLR update, a total of 112 reports were included in the review. Of these, 111 unique studies were identified.

Figure 25 PRISMA flow diagram for Healthcare cost and resource use update



Targeted literature search

N/A

Appendix K. Safety outcomes

Safety outcomes from VISION-DMD

Table 96 Summary of all AEs in Period 1 vs Period 2 in the vamorolone groups (Safety-2 Population)

	Vamorolone 6.0 mg/kg/day	
	Period 1 (N=28)	**Period 2 (N=28)**
TEAEs	25 (89.3)	21 (75.0)
Drug-related TEAEs	19 (67.9)	11 (39.3)
Severe TEAEs	0	2 (7.1)
Serious TEAEs	0	2 (7.1)
TEAEs leading to dose interruption	1 (3.6)	3 (10.7)
TEAEs leading to withdrawal from treatment	0	1 (3.6)
TEAEs leading to withdrawal from study	0	1 (3.6)
TEAEs leading to death	0	0

Abbreviations: TEAE = treatment-emergent adverse event; N = N = number of subjects; mg = milligram; kg = kilogram.

Table 97 Height z-score at Baseline and Week 24 in Period 1 (Safety-1 Population)

Height z-score	Placebo	Prednisone 0.75 mg/kg/day (N=31)	Vamorolone 6.0 mg/kg/day (N=28)
Baseline			
n	29	31	28
Mean (SD)	-0.58 (1.206)	-0.44 (1.025)	-1.04 (1.05)
Median	-0.54	-0.56	-1.04
Min, Max	-2.71, 2.65	-2.24, 1.88	-3.47, 1.02
SEM	0.224	0.184	0.198

Week 24			
n	28	30	26
Mean (SD)	-0.53 (1.242)	-0.50 (0.947)	-0.87 (1.048)
Median	-0.70	-0.48	-0.90
Min, Max	-2.63, 2.94	-2.05, 1.51	-2.86, 1.27
SEM	0.235	0.173	0.206
Week 24 Change from baseline			
n	28	30	26
Mean (SD)	0.10 (0.279)	-0.08 (0.391)	0.18 (0.257)
Median	0.13	-0.10	0.11
Min, Max	-0.78, 0.61	-1.19, 1.09	-0.18, 0.86
SEM	0.053	0.071	0.050

Note: Baseline is defined as the last measurement taken prior to first exposure to study drug, including Day 1 measurements taken predosing. A z-score of 0 represents a normal growth trajectory. Abbreviations: Min = minimum; Max = maximum; mg = milligram; kg = kilogram; SD = Standard Deviation; N = Number of subjects; SEM = Standard error of the mean.

Table 98 Change from baseline in bone biomarkers at Week 24 in the placebo group, prednisone 0.75 mg/kg group and vamorolone 6.0 mg/kg/day group

Change from Baseline at Week 24	Statistic	Placebo (N=29) n (%)	Prednisone 0.75 (N=31) n (%)	Vamorolone 6.0 (N=28) n (%)
Osteocalcin (ng/mL)				
	n	23	23	22
	Mean	-2.89	-15.50	-0.17
	SD	15.43	15.76	17.70
	Median	-3.1	-16.1	0.1
	Min	-26.7	-51.8	-40.7
	Max	31.0	18.6	38.6
	SEM	3.22	3.29	3.77

P1NP (mcg/L)				
	n	23	23	23
	Mean	-39.46	-143.73	-7.93
	SD	138.03	124.57	122.14
	Median	-25.4	-117.0	26.7
	Min	-347.6	-379.6	-242.6
	Max	193.7	109.4	239.2
	SEM	28.78	25.97	25.47
CTX (pg/mL)				
	n	23	24	23
	Mean	20.3	-320.3	110.2
	SD	281.3	174.1	266.9
	Median	110	-322	119
	Min	-547	-594	-395
	Max	442	49	701
	SEM	58.7	35.5	55.7

Note: Baseline is defined as the last measurement taken prior to first exposure to study drug, including Day 1 measurements taken pre-dosing. This table includes summary of bone turnover parameters with SI units. If there was a scheduled test and one or more unscheduled tests assigned to the same time point, the most conservative test (i.e., a test with low or high results) was used. Abbreviations: P1NT = Procollagen 1 N-Terminal Propeptide; CTX = Type 1 Collagen C-Telopeptide; Min = minimum; Max = maximum; mg = milligram; kg = kilogram; SD = Standard Deviation; Sem = Standard error of mean; ng = nanogram; pg = picogram; mL = milliliter; mcg = microgram; L = liter; N = Number of subjects.

Table 99 MMRM analysis of change from baseline in serum biomarkers at Week 24 (SAF-1)

	Comparison	n	LSM (SE)	LSM Difference (SE)	LSM Difference 95% CI	p-value
Osteocalcin (ng/mL)						
	Vamorolone 6.0mg/kg/day vs. Placebo	22 vs. 23	1.5972 (2.8934) vs. -3.7334 (2.8173)	5.3306 (3.9491)	-2.5259, 13.1871	0.1808

	Vamorolone 6.0mg/kg/day vs. Prednisone 0.75mg/kg/day	22 vs. 23	1.5972 (2.8934) vs. -15.5207 (2.7979)	17.1179 (3.9307)	-9.2979, 24.9379	<.0001
P1NT (mcg/L)						
	Vamorolone 6.0mg/kg/day vs. Placebo	23 vs. 23	-18.3371 (22.3855) vs. -43.2227 (22.4760)	24.8856 (31.0572)	36.9045, 86.6757	0.4253
	Vamorolone 6.0mg/kg/day vs. Prednisone 0.75mg/kg/day	23 vs. 23	-18.3371 (22.3855) vs. -147.143 (22.3526)	128.8061 (31.0068)	67.1214, 190.4907	<.0001
CTX (pg/mL)						
	Vamorolone 6.0mg/kg/day vs. Placebo	23 vs. 23	80.4502 (45.1124) vs. 6.0537 (45.0157)	74.3965 (62.0616)	-49.0187, 197.8117	0.2340
	Vamorolone 6.0mg/kg/day vs. Prednisone 0.75mg/kg/day	23 vs. 24	80.4502 (45.1124) vs. -313.300 (44.1723)	393.7500 (61.4232)	271.6281, 515.8719	<.0001

Abbreviations: P1NT = Procollagen 1 N-Terminal Propeptide; CTX = Type 1 Collagen C-Telopeptide; CI = Confidence interval; LSM = Least square mean; SE = Standard error; mg = milligram; kg = kilogram; SD = Standard Deviation; Sem = Standard error of mean; ng = nanogram; pg = picogram; mL = milliliter; mcg = microgram; L = liter; N = Number of subjects.

Table 100 Change from baseline at 48 weeks in bone biomarkers

	Statistic	Vamorolone 6.0mg/kg/day (N=28) n (%)	Prednisone 0.75mg/kg/day + Vamorolone 6.0mg/kg/day (N=15) n (%)	Placebo + Vamorolone 6.0mg/kg/day (N=14) n (%)
Osteocalcin (ng/mL)				
	n	19	11	11
	Mean	9.49	16.14	6.45
	SD	15.37	17.68	10.46

	Median	8.7	13.3	6.8
	Min	-31.1	-10.0	-5.6
	Max	30.4	46.1	24.4
	SEM	3.53	5.33	3.16
P1NT(mcg/L)				
	n	20	11	11
	Mean	24.70	78.66	-47.12
	SD	135.86	142.16	149.27
	Median	26.6	94.6	-34.5
	Min	-181.2	-150.5	-300.7
	Max	296.2	302.7	175.1
	SEM	30.38	42.86	45.01
CTX (pg/mL)				
	n	19	11	11
	Mean	231.3	304.7	202.2
	SD	274.8	217.7	225.6
	Median	229	353	242
	Min	-395	-219	-364
	Max	722	544	461
	SEM	63.1	65.6	68.0

Note: Baseline is defined as the last measurement taken prior to first exposure to study drug, including Day 1 measurements taken pre-dosing. This table includes summary of bone turnover parameters with SI units. If there was a scheduled test and one or more unscheduled tests assigned to the same time point, the most conservative test (i.e., a test with low or high results) was used. Abbreviations: P1NT = Procollagen 1 N-Terminal Propeptide; CTX = Type 1 Collagen C-Telopeptide; Min = minimum; Max = maximum; mg = milligram; kg = kilogram; SD = Standard Deviation; SEM = Standard error of mean; ng = nanogram; pg = picogram; mL = milliliter; mcg = microgram; L = liter; N = Number of subjects.

Safety outcomes from the matched comparison of VISION-DMD and FOR-DMD

Table 101 Overview of TEAEs Over 12 Months in VISION-DMD and FOR-DMD Matched Population

Variable	VISION-DMD	FOR-DMD	
	Vamorolone 6.0 mg/kg/day (N=28) n (%); f (Rate)	Prednisone 0.75 mg/kg/day (N=50) n (%); f (Rate)	Deflazacort 0.90 mg/kg/day (N=56) n (%); f (Rate)
Total number of TEAEs	[redacted]	[redacted]	[redacted]
Serious TEAEs	[redacted]	[redacted]	[redacted]
TEAEs of special interest	[redacted]	[redacted]	[redacted]
TEAEs leading to permanent study treatment discontinuation	[redacted]	[redacted]	[redacted]

Note: Drug-related TEAEs have causality deemed as 'DEFINITE', 'POSSIBLE' or 'PROBABLE'. Clinically-relevant AEs are either at least moderate in severity or leading to withdrawal from study or serious event. Rate is calculated as the number of AEs per patient-year. For FOR-DMD exposure and AEs are limited to 12 Months Visit Date; Abbreviations: AE = adverse event; F = AE case count; TEAE = treatment-emergent adverse event; mg = milligram; kg = kilogram. Source: [83]

Table 102 AEs Leading to Discontinuation in VISION-DMD and FOR-DMD Matched Population

	VISION-DMD	FOR-DMD	
System Organ Class Preferred Term	Vamorolone 6.0 mg/kg/day (N=28) n (%); f (Rate)	Prednisone 0.75 mg/kg/day (N=50) n (%); f (Rate)	Deflazacort 0.90 mg/kg/day (N=56) n (%); f (Rate)
Any TEAE	[redacted]	[redacted]	[redacted]
Endocrine Disorders	[redacted]	[redacted]	[redacted]
Cushingoid	[redacted]	[redacted]	[redacted]
Hepatobiliary Disorders	[redacted]	[redacted]	[redacted]
Hepatitis Acute	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]
Weight Increase	[redacted]	[redacted]	[redacted]

Psychiatric Disorders	[redacted]	[redacted]	[redacted]
Abnormal Behaviour	[redacted]	[redacted]	[redacted]

Note: For VISION-DMD study the population is patients receiving 6.0 mg/kg/day from start of period 1 and who continued to period 2. Rate is calculated as the number of AEs per patient-year. For FOR-DMD exposure and AEs are limited to 12 Months Visit Date; Abbreviations: f = AE case count; TEAE = treatment emergent adverse event; SAE = serious adverse event; mg = milligram; kg = kilogram. Source: [83]

Table 103 Adverse Event Rates by Severity in VISION-DMD and FOR-DMD Matched Population

	Severity	VISION-DMD	FOR-DMD	
		Vamorolone 6.0 mg/kg/day (F=162) f (%)	Prednisone 0.75 mg/kg/day (F=252) f (%)	Deflazacort 0.90 mg/kg/day (F=305) f (%)
Any TEAE	Mild	[redacted]	[redacted]	[redacted]
	Moderate	[redacted]	[redacted]	[redacted]
	Severe	[redacted]	[redacted]	[redacted]
Severe TEAEs				
Cushingoid	Severe	[redacted]	[redacted]	[redacted]
Appendicitis	Severe	[redacted]	[redacted]	[redacted]
Appendicitis Perforated	Severe	[redacted]	[redacted]	[redacted]
Gastroenteritis	Severe	[redacted]	[redacted]	[redacted]
Influenza	Severe	[redacted]	[redacted]	[redacted]
Tonsillitis	Severe	[redacted]	[redacted]	[redacted]
Limb injury	Severe	[redacted]	[redacted]	[redacted]
Weight increased	Severe	[redacted]	[redacted]	[redacted]
Abnormal behaviour	Severe	[redacted]	[redacted]	[redacted]
Asthma	Severe	[redacted]	[redacted]	[redacted]

Note: For VISION-DMD study the population is patients receiving 6.0 mg/kg/day from start of period 1 and who continued to period 2. Rate is calculated as the number of AEs per patient-year For FOR-DMD exposure and AEs are limited to 12 Months Visit Date. Abbreviations: F = AE case count; TEAE = treatment-emergent adverse event; mg = milligram; kg = kilogram. Source: [83]

Table 104 TEAEs in VISION-DMD and FOR-DMD Matched Population by System Organ Class and Most Frequent Preferred Terms (>10% in any group)

System Organ Class Preferred Term	VISION-DMD	FOR-DMD	
	Vamorolone 6.0 mg/kg/day (N=28) n (%); f (Rate)	Prednisone 0.75mg/kg/day (N=50) n (%); f (Rate)	Deflazacort 0.90 mg/kg/day (N=56) n (%); f (Rate)
Blood and Lymphatic System Disorders	[redacted]	[redacted]	[redacted]
Cardiac Disorders	[redacted]	[redacted]	[redacted]
Congenital, Familial And Genetic Disorders	[redacted]	[redacted]	[redacted]
Ear And Labyrinth Disorders	[redacted]	[redacted]	[redacted]
Eye disorders	[redacted]	[redacted]	[redacted]
Gastrointestinal Disorders	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]
Abdominal pain upper	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]
Abdominal Pain	[redacted]	[redacted]	[redacted]
General Disorders And Administration Site Conditions	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]
Hepatobiliary disorders	[redacted]	[redacted]	[redacted]
Immune System Disorders	[redacted]	[redacted]	[redacted]
Infections and Infestations	[redacted]	[redacted]	[redacted]

Nasopharyngitis	[redacted]	[redacted]	[redacted]
Upper Respiratory Tract Infection	[redacted]	[redacted]	[redacted]
Rhinitis	[redacted]	[redacted]	[redacted]
Gastroenteritis Viral	[redacted]	[redacted]	[redacted]
Injury, Poisoning And Procedural Complications	[redacted]	[redacted]	[redacted]
Fall	[redacted]	[redacted]	[redacted]
Metabolism And Nutrition Disorders	[redacted]	[redacted]	[redacted]
Vitamin D Deficiency	[redacted]	[redacted]	[redacted]
Musculoskeletal And Connective Tissue Disorders	[redacted]	[redacted]	[redacted]
Pain In Extremity	[redacted]	[redacted]	[redacted]
Neoplasms Benign, Malignant And Unspecified (Including Cysts And Polyps)	[redacted]	[redacted]	[redacted]
Nervous System Disorders	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]
Psychiatric Disorders	[redacted]	[redacted]	[redacted]
Irritability	[redacted]	[redacted]	[redacted]
Abnormal Behaviour	[redacted]	[redacted]	[redacted]
Renal And Urinary Disorders	[redacted]	[redacted]	[redacted]
Reproductive system and breast disorders	[redacted]	[redacted]	[redacted]

Respiratory, Thoracic And Mediastinal Disorders	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]
Skin And Subcutaneous Tissue Disorders	[redacted]	[redacted]	[redacted]
Hypertrichosis	[redacted]	[redacted]	[redacted]
Surgical and medical procedures	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]

Abbreviations: TEAE = treatment emergent adverse event; mg = milligram; kg = kilogram; N = Number of subjects.
Source [83]

Table 105 Change from baseline in height, height percentile and height z-score in the matched comparison of studies VISION-DMD and FOR-DMD

Variable	VISION-DMD		FOR-DMD	
	Vamorolone 2.0 mg/kg/day	Vamorolone 6.0 mg/kg/day	Prednisone 0.75 mg/kg/day	Deflazacort 0.90 mg/kg/day
Height (cm)				
Baseline				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline to Month 6				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline to Month 12				

n	Xx	Xxx	Xxx	x
Mean (SD)	Xxxxx	Xxxxx	Xxxx	Xxxx
Median	Xxxx	Xxxx	Xxxx	Xxx
Min, Max	Xxxxx	Xxxxx	Xxxx	Xxxxx
Height percentile				
Baseline				
n	Xx	Xxx	Xx	x
Mean (SD)	Xxxx	Xxxxx	Xxxx	Xxxx
Median	Xxx	Xxxx	Xxxx	Xxxx
Min, Max	Xxxxxx	Xxxxxx	Xxxxx	Xxxxx
Change from Baseline to Month 6				
n	Xx	Xx	Xx	Xx
Mean (SD)	Xxxxx	Xxxxx	Xxxxx	Xxxxx
Median	Xxxx	Xxxx	Xxxx	Xxxx
Min, Max	Xxxx	Xxx	Xxx	xx
Change from Baseline to Month 12				
n	Xxx	Xxx	Xxx	Xxx
Mean (SD)	Xxxx	Xxxx	Xxx	Xxx
Median	Xxxx	Xxx	Xxx	Xxx
Min, Max	Xxxx	Xxx	Xxxx	Xxxxx
Height z-score				
Baseline				
n	Xx	x	Xx	xx
Mean (SD)	Xxxx	Xxxxx	Xxxxx	Xxxxx

Median	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline to Month 6				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline to Month 12				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Min = Minimum; Max = Maximum; SD = Standard deviation; cm = centimetre; mg = milligram; kg = kilogram; n = Number of subjects.

Appendix L. Additional scenario analyses

[redacted]

Table 106 [redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Xxx	Xxx	Xxx	Xxxxx	Xxxx
Xxx	Xxx	Xxx	Xxxxx	Xxxx

Xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

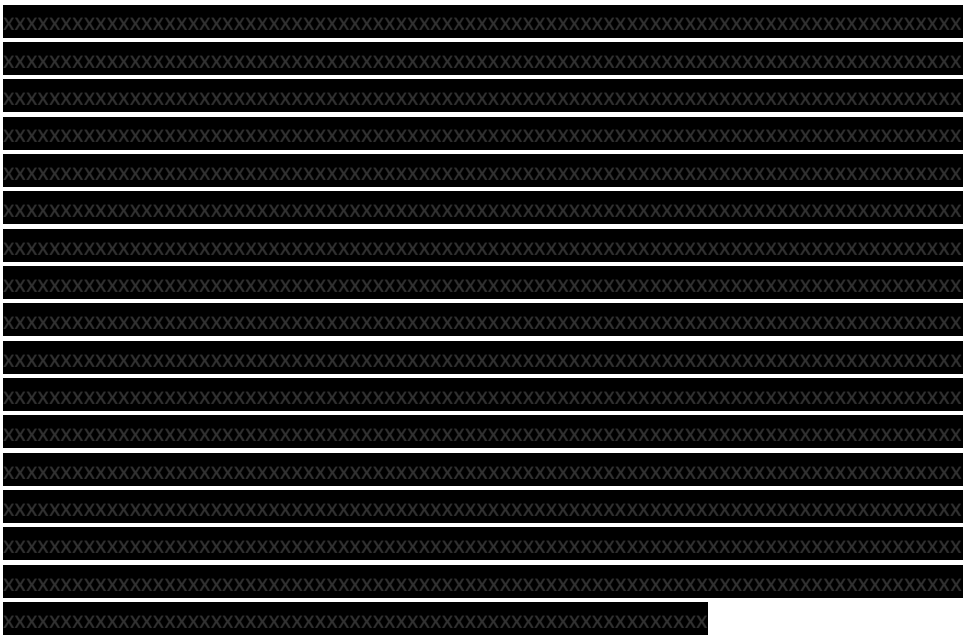
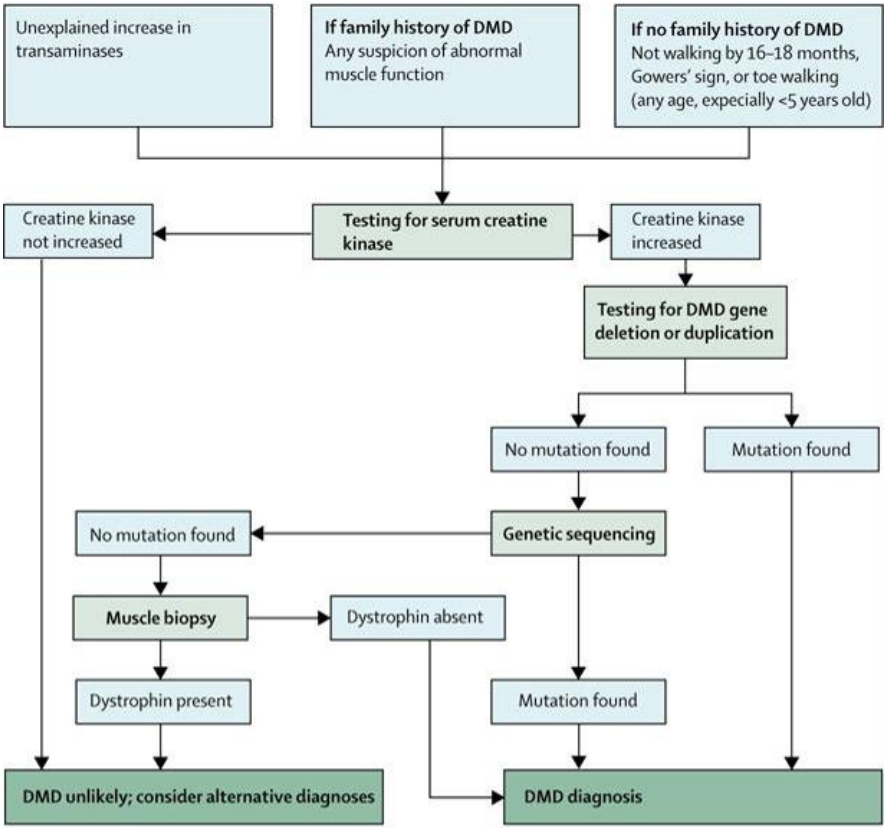


Table 107 xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

Xxxxxxxx	Xxxx	Xxxxxxx	X	x
Xxxxxx	Xxxx	X	Xxxxxx	xxxxxx
Xxxxxx	Xxxxx	Xxxxx	Xxxxxx	xxxx

Appendix M. Diagnosing DMD

Figure 26 Diagnosing DMD



Source: [10]

Appendix N. Cost-effectiveness of the comparators

Table 108 DMC criteria for accepting a relevant comparator in the absence of a prior DMC assessment

Overview of comparator	Glucocorticoid therapy
The comparator can be considered as an established standard Danish treatment practice over a longer period [54]	Glucocorticoid therapy is the standard to care for the treatment of DMD in Denmark, according to clinicians from Aarhus University Hospital [31], Amgros [41] and DMC [38]. Moreover, DMC has previously assessed that the majority of DMD patients receive glucocorticoid treatment [38].

Overview of comparator	Glucocorticoid therapy
If the pharmaceutical has a documented effect on the patient population that is relevant for the assessment by the Danish Medicines Council [54]	Glucocorticoid therapy has demonstrated benefit in both ambulatory and non-ambulatory DMD patients [5-9]. Glucocorticoids are associated with a delay in the loss of mobility, upper limb function [6], pulmonary function [7], and need for scoliosis surgery and ventilation [9]. Despite the benefits, glucocorticoids are associated with potentially serious adverse effects such as osteoporosis, weight gain, cushing syndrome, growth stunting, cataracts [10] that have led to parents deciding not to initiate treatment [38, 112], dose reductions [3, 4, 14], treatment switch and treatment discontinuation [112]. Several studies have demonstrated that sub-optimal doses from down-titrating glucocorticoids by reducing the daily dose or using intermittent dosing result in lower efficacy [5, 15, 16].
Costs of the comparator are low [54]	Prednisolone has generics available and is sold by multiple companies. One example is Prednisolone “Actavis" 25 mg by Teva, which has an apotekernes indkøbspris (AIP) of 127 DKK (1 pack has 100 capsules) as of 17 January 2025. [113]. Deflazacort 6 mg by Vital Pharma Nordic has an AIP of 845 DKK (1 pack has 60 capsules) as of 17 January 2025 [53].

Abbreviations: DMC = Danish Medicines Council; AIP = pharmacy wholesale price; DKK = Danish krona; mg = milligram; kg = kilogram.

Appendix O. Details on efficacy measures relevant for the application

Table 109 Efficacy outcome measures relevant for the application (additional details)

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
VISION-DMD			
TTSTAND (Time to stand from supine)	[redacted]	[redacted]	[redacted]

TTCLIMB (Time to climb 4 steps)	[redacted]	[redacted]	[redacted]
TTRW (Time to Run/Walk 10 meters)	[redacted]	[redacted]	[redacted]
NSAA (North Star Ambulatory Assessment)	[redacted]	[redacted]	[redacted]
6MWT (6 Minute Walk Test)	[redacted]	[redacted]	[redacted]

FOR-DMD

Rise from the floor velocity	[redacted]	[redacted]	[redacted]
(TTSTAND velocity)			

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

[a] Descriptive statistics are based on observed cases (without multiple imputation).

[b] The LSM estimates are derived from a restricted maximum likelihood (REML)-based MMRM model with enrollment stratification age group (4-5 years; 6-<7 years), treatment (vamorolone 2.0 mg/kg/day, vamorolone 6.0 mg/kg/day, prednisone 0.75 mg/kg/day, and placebo), week, baseline response, and the treatment-by-week interaction. Study week was included in the model as a categorical variable (Weeks 6, 12, and 24) along with the treatment-by-week interaction. An unstructured covariance structure was used and the Kenward-Roger approximation was used to estimate denominator degrees of freedom

Abbreviations: MCID = minimal clinically important difference; MMRM = Mixed model repeated measures; LSM = Least square means; REML = restricted maximum likelihood; TTRF = Time taken to rise from the floor.

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