Medicinrådet

Bilag til Medicinrådets vurdering af bulevirtid til behandling af kronisk hepatitis D

Vers. 1.0

Bilagsoversigt

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

GILEAD

Høringsbrev vedr. vurdering af bulevertid (Hepcludex) til behandling af HDV

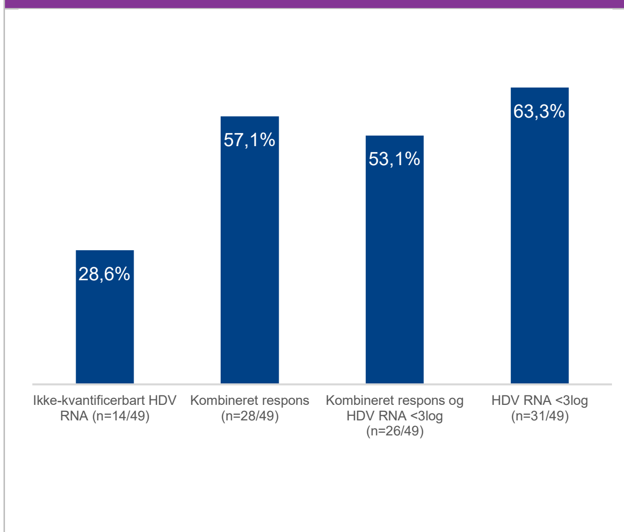
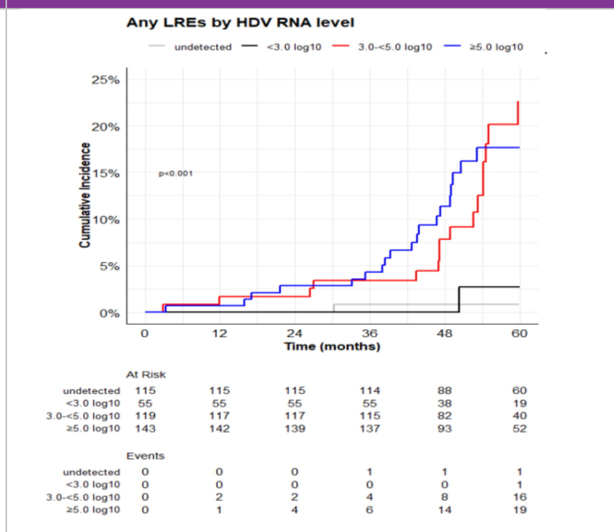
Scenarie 2 er ikke klinisk relevant og bør udgå:

Medicinrådet har valgt at konstruere 2 scenarier i deres sundhedsøkonomiske evaluering. I dette afsnit vil Gileads Sciences forklare hvorfor scenarie 2 er klinisk implausibelt og bør fjernes fra vurderingsrapporten.

Gilead Sciences er enig med Medicinrådet i, at "*patienter med ikke-kvantificerbart HDV-RNA niveau vil have bedre prognose sammenlignet med patienter med* ***reduktion*** *af HDV-RNA* ***på minimum 2log10*** *IU/ml* ***ift. baseline***"

Problemet består i, at modelleringen i scenarie 2 kun tilskriver behandlingseffekt af bulevirtid ved opnåelse af et ikke-kvantificerbart HDV-RNA niveau, og det er fejlagtigt at antage. Vi henleder Medicinrådets opmærksomhed på RWE fra Kamal et al. 2025 i figur 2 nedenfor fra Delta Cure konferencen i 2025 [1]. Patienter med absolutte HDV RNA værdier ≥3-<5log10 IE/ml [rød kurve i figur 2] og ≥5log10 IE/ml [blå kurve i figur 2] har en højere risiko for lever relaterede events (LREs). Forskellen mellem ikke-kvantificerbart HDV-RNA niveau [lysergrå kurve i figur 2] og HDV RNA <3log10 IE/ml [sort kurve i figur 2] er dog forsvindende lille.

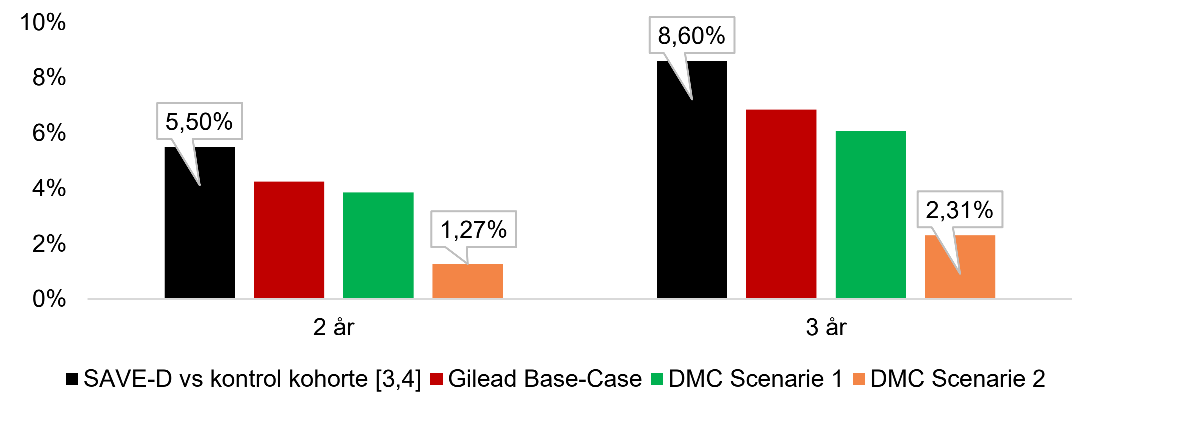
Ved uge 144 i MYR301 havde 28,6 % opnået ikke-kvantificerbart HDV-RNA niveau mens 63,3% opnåede abolutte HDV RNA værdier <3log10 IE/ml), se figur 1. Implikationen af dette er, at Medicinrådet i scenarie 2 ikke tilskriver nogen effekt til de 34,7%-point af patienterne (63,3%-28,6%) som havde HDV RNA <3log10 IE/ml [sort kurve i figur 2]. D-SOLVE data fra EASL konferencen i 2025 [2], som allerede indgår i Medicinrådets evaluering, viser præcis det samme.

Figur 1 Uge 144 resultater fra MYR301	Figur 2 Kumulativ incidens af LRE
	
Kilde: MYR301, data on file	Kilde: Kamal et al. 2025 [1]

Implikation af den fejlagtige antagelse om at effekten kun følger patienter med ikke-kvantificerbart HDV-RNA niveau forplanter sig til modelleringen af LRE i modellen og skaber reduktionen i QALY gevinsten. I figur 3 nedenfor illustreres det hvorledes dette fører til en voldsom underestimering af behandlingseffekten af bulevirtid, på De Novo dekompensering for patienter med cirrose.

I Medicinrådets scenarie 1, og i Gilead Sciences ansøgning, beregnes effekt ud fra kombineret response som er 57,1% ved 144 uger. Figur 3 nedenfor illustrerer, at det havde været mere klinisk relevant med et sceanarie hvor behandlingseffekt øges til 63,3% (svarende til andelen af patienter der opnåede HDV RNA <3log10 IE/ml) da både DMCs scenarie 1 og Gilead Sciences hovedanalyse undervurderer den absolutte reduktion i LREs ift. RWE.

Figur 3 Forskel (BSC-BLV) i De Novo dekompensering for patienter med cirrose



Kilde: Degasperi et al. 2024: 2 år [3], og Degasperi et al. 2026: 3 år [4].

Scenarie 2 er ikke korrekt modelleret:

Fraset at analysen ikke er klinisk relevant, så er omkostningerne modelleret fejlagtigt i scenarie 2. Ifm. at modellen blev justeret til at antage, at der kun er behandlingseffekt ved opnåelse af ikke-kvantificerbart HDV-RNA niveau er det blevet overset, at raterne for hvor mange det kan antages at stoppe behandlingen bestandigt ikke er blevet opdateret. Patienter 'uden respons' [dvs. kvantificerbart HDV-RNA i scenarie 2] stoppes alle ved uge 144, men Medicinrådet har overset, at sandsynlighederne for at kunne stoppe behandling, som følge af ikke-kvantificerbart HDV-RNA niveau i mere end 96 uger, ikke er blevet justeret i modellen. Rettes dette reduceres ICER med ca. 400.000 kr til 1.250.000 kr/QALY i scenarie 2 og ligner til forveksling scenarie 1.

Alvorlighedprincippet bør aktiveres:
Gilead Sciences mener, af flere årsager, at Rådet bør aktivere alvorlighedsprincippet i denne sag. Medicinrådet og Gilead Sciences er enige om, at sygdommen er alvorlig, at patienterne er yngre (36 år i gennemsnit), og at der ikke er andre behandlingsalternativer når (off-label) interferon har været forsøgt, og endeligt at behandlingen er et betydeligt fremskridt. Patienter, som modtager behandling med bulevirtid opnår et betydeligt ekstra antal QALYs sammenlignet med når patienterne blot modtager 'best supportive care'. Baseret på Medicinrådets scenarie 1 beregnes en QALY forskel på 3,66 diskonteret og 8,48 udiskonteret.

Alvorligheden kan f.eks. kvantificeres ved hjælp af absolut prognose tab, og her ligger HDV i den absolut høje ende. Det absolutte prognosetab for HDV er 30 QALYs, når dette beregnes ud fra Medicinrådets scenarier.

Referencer:
[1] H. Kamal et al., "Course and Clinical Outcomes of Chronic Hepatitis Delta: A Longitudinal Analysis of 565 Patients from the D-SOLVE Consortium and HDV1000 Database," p. Delta Cure 2025: Abstract ID: 77 Poster ID: 42, 2025.

[2] H. Kamal et al., "Course and Clinical Outcomes of Chronic Hepatitis Delta: A Longitudinal Analysis of 565 Patients from the D-SOLVE Consortium and HDV1000 Database," J. Hepatol., vol. 82S1, pp. S1-S966: Oral OS-068, EASL 2025, 2025.

[3] E. Degasperi et al., "Bulevirtide Monotherapy prevents liver decompensation and reduces mortality in patients with HDV-realted cirrhosis: a case-control study with propensity score weighted analysis," J. Hepatol., p. EASL Congress 2024: OS-120, 2024, doi: 10.1053/j.gastro.2009.01.052.

[4] E. Degasperi et al., "Bulevirtide monotherapy prevents liver decompensation in patients with hdv-related cirrhosis: a case control study with propensity score weighted analysis," J. Hepatol., vol. 84S1, pp. S69–S981-TOP-582, 2026.

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28.05.2026

LSC/DBS

Forhandlingsnotat

Dato for vurdering i Medicinrådet	24.06.2026
Leverandør	Gilead Sciences
Lægemiddel	Hepcludex (bulevirtid)
Ansøgt indikation	Behandling af kronisk hepatitis delta-virus (HDV) infektion i plasma (eller serum) HDV-RNA-positive voksne og børn fra 3 år, der vejer minimum 10 kg, med kompenseret leversygdom
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende pris på Hepcludex:

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke (pakning)	AIP (DKK)	Nuværende SAIP (DKK)	Nuværende rabat ift. AIP	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Hepcludex	2 mg (30 stk.)	52.632,00	[redacted]	[redacted]	[redacted]	[redacted]

Prisen er betinget af Medicinrådets anbefaling. Det betyder, at hvis Medicinrådet ikke anbefaler Hepcludex, indkøbes lægemidlet til nuværende SAIP.

Aftaleforhold

Amgros har en eksisterende aftale på Hepcludex. Aftalen gælder til den 31.03.2027 med mulighed for at forlænge i 2x12 måneder.
[redacted]

Informationer fra forhandlingen

[redacted]

Konkurrencesituationen

Medicinrådet har ikke anbefalet andre lægemidler som standardbehandling til patienter med kronisk hepatitis delta-virus (HDV), der har oplevet relaps efter, eller ikke tåler, behandling med pegyleret interferon alfa-2a (den ansøgte population).

Tabel 2 viser de årlige lægemiddeludgifter ved behandling med Hepcludex.

Tabel 2: Lægemiddeludgifter pr. patient

Lægemiddel	Styrke (pakning)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Hepcludex	2 mg (30 stk.)	2 mg dagligt, s.c.	[redacted]	[redacted]

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status		Link
Norge	Delvis anbefaling	Patienter med kompenseret leversygdom i fibrosestadier F3 eller F4	Link til vurdering
Sverige	Delvis anbefaling	Patienter med kompenseret leversygdom i fibrosestadier F3 eller F4	Link til vurdering
England	Delvis anbefaling	Patienter med signifikant fibrose eller patienter der ikke responderer på peginterferon alfa-2a	Link til vurdering

Opsummering

Amgros har en aftale på Hepcludex der gælder frem til 31.03.2027.
[redacted]

Application for the assessment of Hepcludex® (bulevirtide) for the treatment of chronic hepatitis delta virus (HDV) infection

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

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Title Phone number E-mail	

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Abbreviations

Abbreviation	Definition
AASLD	American Association for the Study of Liver Diseases
ADA	Anti-drug-antibody
AE	Adverse event
AEMPS	Agencia Española de Medicamentos y Productos Sanitarios
AGENAS	Agenzia Nazionale per i Servizi Sanitari Regionali
AIC	Akaike information criterion
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ASCO	American Society of Clinical Oncology
ASH	American Society of Hematology
AST	Aspartate aminotransferase
ATMP	Advanced Therapy Medicinal Product
AWMSG	All Wales Medicines Strategy Group
BIC	Bayesian information criterion
BLV	Bulevirtide
BMI	Body mass index
BSC	Best supportive care
CADTH	Canadian Agency for Drugs and Technologies in Health
CC	Compensated cirrhosis
CDSR	Cochrane Database of Systematic Reviews
CEA	Cost-effectiveness analysis
CENTRAL	Cochrane central register of controlled trials

CHB	Chronic hepatitis B
CHD	Chronic hepatitis delta
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CLAD	Censored Least Absolute Deviation
CLDQ	Chronic liver disease questionnaire
CRD	Centre for Reviews and Dissemination
DCC	Decompensated cirrhosis
DK	Denmark
DKK	Danish krona
DMC	Danish Medicines Council
DNA	Deoxyribonucleic acid
DSGH	Danish Society for Gastroenterology and Hepatology
DT	Delayed treatment
EASL	European Association for the study of Liver Diseases
EC	European Commission
ECCMID	European Congress for Clinical Microbiology and Infectious Diseases
EED	Economic Evaluation Database
EMA	European Medicines Agency
EOS	End of study
EOT	End of treatment
EPAR	European public assessment report
EQ-5D-3L	EuroQol 5-Dimension, 3-Level
EQ VAS	EuroQol Visual Analogue Scale
FAS	Full analysis set
FDA	Food and Drug Administration
FSS	Fatigue severity scale
GGT	Gamma glutamyl transferase

HAS	Haute Autorité de Santé
HBcrAg	Hepatitis B core-related antigen
HBsAg	HBV surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCRU	Healthcare resources utilisation
HCV	Hepatitis C virus
HDV	Hepatitis delta virus
HIV	Human immunodeficiency virus
HQLQ	Hepatitis Quality of Life
HR	Hazard ratio
HRQoL	Health related quality of life
HS	Health state
HSUV	Health state utility value
HTA	Health technology assessment
HUI	Health utilities index
ICER	Incremental cost-effectiveness ratio
ICTRP	International Clinical Trials Registry Platform
IFN	Interferon
INR	International normalised ratio
IQR	Interquartile range
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ISRCTN	International Standard Randomised Controlled Trial Number
IU	International unit
LLOQ	Lower limit of quantification
LOCF	Last observation carried forward
LOD	Limit of detection
LS	Least square

LT	Liver transplant
LY	Life years
MCID	Minimal clinically important difference
MEF	Missing equals failure
MHLW	Ministry of Health, Labour and Welfare
MMRM	Mixed-effects model for repeated measures
MVR	Maintained virologic response
NA	Nucleoside/nucleotide analogue
N/A	Not applicable
NC	Non-cirrhotic
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NR	Not reported
NTCP	Sodium taurocholate co-transport polypeptide
NYHA	New York Heart Association
OR	Odds ratio
PBAC	Pharmaceutical Benefits Advisory Committee
PCR	Polymerase chain reaction
PICO	Population, Intervention, Comparator, Outcome
PLT	Post-liver transplant
PP	Per protocol
PRO	Patient-reported outcome
PSA	Probabilistic sensitivity analysis
PT	Preferred term
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RDI	Relative dose intensity
RNA	Ribonucleic acid

RRD	Response rate difference
SAE	Serious adverse event
SAS	Safety analysis set
SD	Standard deviation
SE	Standard error
SF-36	Short Form-36 Health Survey
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SOC	System organ class
TEAE	Treatment emergent adverse event
TP	Transition probability
TSH	Thyroid stimulating hormone
UC	Unlimited company
UK	United Kingdom
VR	Virologic responder
WBC	White blood cell
WHO	World Health Organisation

1. Regulatory information on the medicine

Proprietary name	Hepcludex®
Generic name	Bulevirtide
Therapeutic indication as defined by EMA	Bulevirtide is indicated for the treatment of chronic hepatitis delta virus (HDV) infection in plasma (or serum) HDV-RNA positive adult and paediatric patients 3 years of age and older weighing at least 10 kg with compensated liver disease.
Marketing authorization holder in Denmark	Gilead Sciences Ireland UC
ATC code	J05AX28
Combination therapy and/or co-medication	No combination therapy required. Hepcludex (bulevirtide) should be administered as monotherapy or in co-administration with a nucleoside/nucleotide analogue for treatment of underlying hepatitis B virus (HBV) infection.
Date of EC approval	Hepcludex (bulevirtide) received a conditional marketing authorisation on 31 July 2020. The conditional marketing authorisation was changed to a standard marketing authorisation on 18 July 2023.
Has the medicine received a conditional marketing authorization?	Yes, however, the conditional approval has been converted to standard market authorisation.
Accelerated assessment in the European Medicines Agency (EMA)	Initially, however accelerated assessment was terminated during assessment by the CHMP (1).
Orphan drug designation (include date)	Yes (19 June 2015)
Other therapeutic indications approved by EMA	No
Other indications that have been evaluated by the DMC (yes/no)	No

Joint Nordic assessment (JNHB)	Are the current treatment practices similar across the Nordic countries (DK, FI, IS, NO, SE)? [yes/no] No, Norway and Sweden have Hepcludex reimbursed and in routine use. Is the product suitable for a joint Nordic assessment? [yes/no] If no, why not? No, bulevirtide was already assessed in Norway and Sweden.
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	Vial, 2 mg powder for solution for injection, 30 vials per pack

2. Summary table

Summary	
Indication relevant for the assessment	Bulevirtide is indicated for the treatment of chronic hepatitis delta virus (HDV) infection in plasma (or serum) HDV-RNA positive adults and paediatric patients 3 years of age and older weighing at least 10 kg with compensated liver disease. The patient population relevant for assessment is limited to patients in fibrosis stages F2 or F3 who are ineligible for pegIFN-α or who have already attempted pegIFN-α treatment without effect, or patients who are cirrhotic.
Dosage regiment and administration	2 mg once daily by subcutaneous injection.
Choice of comparator	No active treatment + best supportive care
Prognosis with current treatment (comparator)	Only approximately 10% of patients with chronic hepatitis delta (CHD) achieve recovery. Among those who do not recover in the early stages, HDV infection drives a rapid progression to fibrosis, earlier liver decompensation with cirrhosis, and a higher risk of hepatocellular carcinoma (HCC)—resulting in increased liver-related mortality. The 5- and 10- year survival rate of HDV patients without liver decompensation and/or HCC is 96.8% and 81.9%, respectively; whereas this decreases with cirrhosis (but still without HCC) to 83.9% and 59.4%, respectively (2). Co-infection (HBV+HDV) doubles the mortality risk relative to HBV mono-infection (RR: 2.0; 95% CI: 0.7, 5.7) (3).
Type of evidence for the clinical evaluation	Head-to-head study.

Most important efficacy endpoints (Difference/gain compared to comparator)	**Percentage of participants with combined response:*** bulevirtide 2 mg after 48, 96, 144 and 240# weeks: 44.9%, 55.1%, 57.1%, and 24.5%#, respectively. BSC after 48 weeks: 2%. Response rate difference at 48 weeks: 42.9% (96% CI 27.0, 58.5). **Percentage of participants with undetectable HDV RNA:** bulevirtide 2 mg after 48, 96, 144 and 240# weeks: 12.2%, 20.4%, 28.6%, and 20.4%, respectively. BSC after 48 weeks: 0%. Response rate difference at 48 weeks: 12.2% (95% CI 2.9, 21.5). **Virologic response:** bulevirtide 2 mg after 48, 96, 144 and 240# weeks: 73.5%, 75.5%, 73.5%, and 32.7%#, respectively. BSC after 48 weeks: 3.9%. Response rate difference at 48 weeks: 69.5% (95% CI 54.1, 81.9). **Change from baseline in liver stiffness** (LS mean): bulevirtide 2 mg after 48, 96, 144 and 240# weeks: -3.06, -4.31, -5.24, and -1.2#, respectively. BSC after 48 weeks: 0.87. Response rate difference at 48 weeks: -3.93 (95% CI -6.23, -1.63). *Defined as undetectable HDV RNA (defined as HDV RNA <LLoD, where LLoD=6 IU/mL) or decrease by ≥2 log10 IU/ml from baseline and ALT normalisation (defined as an ALT value within the normal range). # The Week 240 time point reflects a follow-up period of 96 weeks after completion of the 144-week treatment period.
Most important serious adverse events for the intervention and comparator	SAEs after 48 and 144 weeks in the bulevirtide 2 mg arm n=2 (4%) and 3 (6%), respectively. BSC after 48 weeks n=1 (2%). None of the SAEs while on treatment were considered related to study drug by the investigators.
Impact on health-related quality of life	**EQ-5D Index score**: Mean change from baseline (95% CI) Week 24: bulevirtide 0.05 (0.02,0.09) vs. BSC 0.02 (-0.02,0.07) Week 40: 0.04 (0.00,0.07) vs. 0.03 (-0.02,0.08) Week 48: 0.05 (0.01,0.08) vs. 0.05 (0.00,0.09) Bulevirtide only reporting for week 72: 0.07 (0.04,0.10), week 96: 0.06 (0.02,0.10), week 144: 0.07 (0.03,0.11).
Type of economic analysis that is submitted	Type of analysis: Cost-utility Type of model: Decision tree followed by a Markov model
Data sources used to model the clinical effects	MYR301 clinical trial
Data sources used to model the health-related quality of life	MYR301 clinical trial
Life years gained	4.67 years
QALYs gained	4.36 QALY
Incremental costs	3 978 241 DKK

ICER (DKK/QALY)	912 105 DKK/QALY
Uncertainty associated with the ICER estimate	Based on the deterministic sensitivity analysis, the most influential is Hepcludex adherence. The second most is the response of the composite endpoint at week 96 among patients on Hepcludex treatment. The third most influential parameter is the modelled health state utility in F2 for responders.
Number of eligible patients in Denmark	Incidence: less than 5 per year Prevalence: 40
Budget impact (in year 5)	10 million DKK

Abbreviations: BSC = best supportive care; CHD = chronic hepatitis delta; DKK = Danish krona; EQ-5D-3L = EuroQol 5-Dimension, 3-Level; EQ VAS = EuroQol Visual Analogue Scale; HCC = hepatocellular carcinoma; HQLQ = Hepatitis Quality of Life; HDV = hepatitis delta virus; QALY = quality-adjusted life year; SAE = serious adverse event

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

3.1 The medical condition

3.1.1 Disease description

HDV is an incomplete RNA virus that depends on the HBV for entry into hepatocytes and replication, classifying it as a "satellite virus" (4, 5). As a result, HDV infection occurs only in individuals who are concomitantly infected with HBV, either through HBV/HDV coinfection or through HDV superinfection in patients with chronic HBV (6, 7). Coinfection commonly results in an acute infection which usually resolves rapidly (with <5% of infections becoming chronic), whereas superinfection can progress to chronic hepatitis delta (CHD), which exacerbates any pre-existing HBV-related liver damage (7, 8). Acute infection may present with a spectrum of symptoms including fever, fatigue, loss of appetite, nausea, vomiting, abdominal pain, dark urine, clay-coloured stools, joint pain, and jaundice, along with biochemical evidence of liver injury, such as elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels (7, 8). Chronic HDV infection, which might be non-symptomatic compared to chronic disease, is defined as persistence of infection for six months or longer, and the risk of progression to chronic hepatitis varies markedly depending on the mode of initial infection (8-10). Fewer than 5% of individuals develop chronic infection following coinfection, whereas more than 80% of those with HDV superinfection progress to chronic disease (8). CHD may manifest with a wide range of clinical presentations, from subtle, non-specific symptoms to rapidly advancing liver dysfunction, and often exacerbates pre-existing HBV-related liver disease. ALT and AST elevations are typically persistent, and many cases are diagnosed incidentally or only after the onset of late complications (7), such as cirrhosis and HCC, which contribute to increased morbidity and mortality (11-13).

3.1.2 Pathophysiology

HDV only replicates in the liver, and therefore pathological changes are limited to this organ. However, the HDV virion is assembly-deficient, requiring an envelope provided by HBV in order to enter host cells; thus, HDV is assumed to enter hepatocytes through the same mechanism as HBV (14). The entry of both HBV and HDV into host cells requires the attachment of a surface protein found within the N-terminal myristoylated domain of the HBV envelope L-protein to sodium taurocholate co-transport polypeptide (NTCP), a hepatic bile salt transporter, followed by subsequent entry and membrane fusion (15, 16).

Although the exact pathologic mechanisms are unknown, the immune system is implicated in HDV-associated liver damage, through interferon (IFN)-α signalling inhibition, HDV-specific T-lymphocyte activation, as well as cytokine and transcription factor signalling (7). This inflammatory response causes liver swelling, which can impair liver functioning and cause long-term problems such as liver scarring (fibrosis, and ultimately cirrhosis), associated with an excessive accumulation of extracellular matrix proteins such as collagen which is the result of the wound-healing response of the liver to repeated injury (such as viral hepatitis), as well as liver failure and HCC (9). However, multiple studies have previously shown that liver scarring is reversible under treatment (see Section 8.1.2.3.3 for more information) (17, 18). Individuals with cirrhosis can remain complication-free for a few years (compensated cirrhosis [CC]), followed by the development of complications from portal hypertension and/or liver dysfunction (decompensated cirrhosis [DCC]) (19). DCC is associated with short survival, with liver transplantation (LT) often indicated as the only effective therapy (20).

3.1.3 Patient prognosis and impact on QoL

3.1.3.1 Patient prognosis

Patient prognosis in patients with HDV infections strongly depends on how the disease progresses. The disease course often begins with hepatitis flares during early infection, followed by a decline in HDV replication and subsequent reactivation of HBV (21). However, once infected, recovery is rare and the likelihood of recovery decreases as the disease progresses. Only 35% of people with acute infection (0 to 6 months after infection) recover, and this number drops to just 9.96% among those with CHD infection (starting from 6 months after infection) (22). Over half (52%) of those with acute HDV infection progress to CHD (22). In some cases, this transition occurs rapidly - approximately 39.2% (95% CI: 13.14, 69.16) of acutely infected individuals develop chronic hepatitis within an average of 1.5 years (range: 1.0-1.7 years) (22). Among individuals who develop CHD infection, 76.47% (95% CI: 63.98, 86.98) advance to chronic, symptomatic, disease within just three years (22).

As the disease advances, long-term outcomes worsen considerably. Patients who do not recover in the early stages experience rapid liver deterioration, marked by accelerated fibrosis, early decompensation with cirrhosis, and an elevated risk (pooled odds ratio: 1.28; 95% CI: 1.05,1.57; compared to HBV only) of HCC. Consequently, HDV infection results in substantially greater liver-related mortality compared to hepatitis B (12, 23, 24). Indeed, up to 80% of people with CHD progress to cirrhosis within 5–10 years and about 10 to 15% of patients progress within just two years (19, 25). A meta-analysis of 11 prospective studies by Alfaiate et al. (24) investigating HCC development in HDV infected individuals compared to individuals with HBV mono-infection reported a pooled odds ratio of 2.77. In a recent trial, the cumulative incidence of HCC in patients with simultaneous HBV and HDV infection versus patients with only HBV at 1, 3, and 5 years was 5.2%, 11.8%, and 20.2% versus 1.1%, 2.5%, and 4.4% (subhazard ratio, 4.99; 95% CI, 2.36–10.52; p <.001), respectively (26). On a global scale, HDV coinfection is estimated to account for one in five to one in six cases of cirrhosis or HCC among individuals with HBV (27, 28).

Of patients dying from progressive HDV infection, nearly 60% die from liver failure and overall mortality rates are significantly higher than among HBV-infected individuals (29). Moreover, 10.91% of people with chronic infection die within the first six months, compared with only 1.21% of those with acute infection (22). Conclusively, hepatitis delta carries the highest mortality rate (20%) when compared to any other viral hepatitis (3, 21).

3.1.3.2 Impact on QoL

Beyond its clinical impact, HDV imposes a substantial burden on health-related quality of life (HRQoL). Average EQ-5D scores are approximately 0.81, while visual analogue scale (VAS) scores average 0.64 (30). Nearly half of affected individuals report moderate to severe restrictions in daily functioning and overall well-being. Treatment can further affect QoL which was described by a Turkish study applying the Beck Depression Inventory-II, which found high depression scores among all participants during and after pegylated interferon-alpha (pegIFN-α) therapy (31). Furthermore, HDV coinfection is associated with more pronounced abdominal symptoms, greater daily impairment, and lower functional well-being than population norms, based on patients with CHD completing the Chronic Liver Disease, Functional Assessment of Chronic Illness Therapy–Fatigue, and Work Productivity and Activity Impairment questionnaires (32, 33).

3.2 Patient population

A recent analysis from Watson et al. Watson, Jepsen (34) estimated that 3.1% of individuals with chronic HBV in Denmark are coinfected with HDV, corresponding to a prevalence of approximately 4 cases per 100,000 inhabitants. In 2024, a prevalence of 241 patients were identified in Denmark (Table 1) (34). Incidence was estimated using the HBV incidence in Denmark multiplied with the 3.1% coinfection rate reported by Watson et al.

In the MYR301 clinical trial of adult CHD patients, the age of patients ranged from 19 years to 62 years old (35). Although not tested in the MYR301 trial, collected data suggests that bulevirtide will be effective in the treatment of chronic HDV infection in children from 3 years of age, justifying their inclusion into the indication (36), which is described in Table 3. This is further supported by previous observation of development of cirrhosis in paediatric patients with HDV by Xue, Glenn (37). Kamal, Westman (38) reported the age for HDV patients in Sweden, which was confirmed as relevant for the mean age of Swedish patients by Swedish clinical expert input (39). As there is no data reported on this for Denmark, Kamal, Westman (38) is assumed to be relevant for Denmark as well, resulting in an average age of 36.3 years in Denmark, of which patients in the F2 fibrosis stage are commonly younger than patients in the F3 or F4 stages. Based on the same assumptions, approximately 51% of patients are male (38, 39).

Table 1 Incidence and prevalence in the past 5 years

	2020	2021	2022	2023	2024
HBV Incidence in Denmark (40)	**153**	**121**	**101**	**106**	**132**
Estimated* HDV Incidence in Denmark	5	4	3	3	4
HDV Prevalence in Denmark (34)	NR	NR	NR	NR	241
Global prevalence	Not relevant				

Abbreviations: HBV = hepatitis B virus; HDV = hepatitis delta virus; NR = Not reported

*HDV incidence estimated using the finding that 3.1% of HBV were coinfected with HDV (34)

According to Danish guidelines, patients ineligible for pegIFN-α or who have already attempted pegIFN-α treatment, and with fibrosis stages F2 to F4 could be considered eligible for bulevirtide treatment (41). However, no public data is available regarding the distribution and progression of fibrosis, including the development of cirrhosis, in CHD for Denmark. Therefore, patient estimates for Denmark are based on insights from Sweden.

Notably, there is a difference in expected patient numbers between Sweden and Denmark, not only due to difference in population, but also due to difference in number of patients with chronic hepatitis B. Watson, Jepsen (34) reported 7,878 patients with chronic hepatitis B in Denmark and Colombe, Axelsson (42) reported a 0.21% prevalence in Sweden which is equivalent to 22,270 patients. For the purpose of this estimate, we assume the HDV coinfection rates to be comparable between countries.

Of patients diagnosed with CHD in Sweden, it was estimated that [redacted] of patients are at F2 fibrosis stage whereas [redacted] are at the stages F3 and F4, respectively (43). Two years after positive reimbursement in Sweden, [redacted] and as of October 2025, [redacted] patients are in bulevirtide treatment in Sweden across F3 and F4 stages. For the purpose of this estimate, we assume the treatment rate would be equal across F stages.

Consequentially, the number of eligible patients in Denmark would be [redacted] * (7,878 / 22,270) which is approximately 40 patients.

As the incidence of new HDV is estimated to be very low, with less than five per year across F stages (Table 1), the assumption is that the pool of eligible patients increases by 1 patient per year (Table 2).

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	41	42	43	44	45

3.3 Current treatment options

PegIFN-α is recommended as a possible treatment option for people with HBV coinfected with HDV by the Danish Society for Gastroenterology and Hepatology (DSGH), supported by the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) (41, 44, 45). However, pegIFN-α is not indicated for the treatment of HDV and formally an off-label treatment.

In Denmark, treatment should be initiated when liver biopsy reveals an inflammation grade of ≥A2 and/or a fibrosis stage of ≥F2 (41). Off-label treatment with pegIFN-α therapy results in some impact on liver histology, such as improvement in fibrosis and clearance of HDV, decreased risk of liver decompensation or need for LT, as well as overall survival (17). However, of those who do receive treatment, only 25% respond to therapy, and they rarely maintain sustained viral suppression (45, 46). Moreover, approximately 50% of HDV patients who receive pegIFN-α therapy experience relapse (47). Furthermore, treatment with pegIFN-α is associated with side effects, including flu-like symptoms, nausea, insomnia, and depression, frequently leading to treatment discontinuation (46). Many people with HDV are also ineligible for pegIFN-α therapy due to contraindications or advanced liver disease (45, 48). Due to these limitations, many people with HDV do not receive any treatment (21).

Accordingly, for patients that reach end-stage liver disease, LT remains the only effective treatment to reverse irreversible liver injury caused by HDV/HBV coinfection (49-51). However, the LT procedure itself and associated drugs used to prevent rejection of the donor liver carry substantial risks, including bleeding, blood clots, infection, mental confusion, seizures, and rejection of the donor liver. Further, side effects associated with anti-rejection medications, which are required for the lifetime of the individual following

LT, include bone thinning, diabetes, headaches, and high blood pressure and cholesterol (6).

Conclusively, no effective treatment for CHD is available in Denmark for patients who discontinue pegIFN-α due to side-effects, relapse on pegIFN-α, or who are ineligible for pegIFN-α treatment.

3.4 The intervention

Bulevirtide (Hepcludex®) is a novel, first-in-disease and first-in-class entry inhibitor used to treat hepatitis delta (4, 15).

Table 3 Overview of bulevirtide

<table>
<tr><th colspan="2">Overview of intervention</th></tr>
<tr><td>Indication relevant for the assessment</td><td>Hepcludex is indicated for the treatment of chronic hepatitis delta virus (HDV) infection in plasma (or serum) HDV-RNA positive adult and paediatric patients 3 years of age and older weighing at least 10 kg with compensated liver disease.

Given the above mentioned approved label and the Danish treatment guidance, the indication relevant for the assessment are patients in fibrosis stages F2 or F3 who are ineligible for pegIFN-α or who have already attempted pegIFN-α treatment without effect, or patients who are cirrhotic (41).</td></tr>
<tr><td>ATMP</td><td>Not applicable.</td></tr>
<tr><td>Method of administration</td><td>Subcutaneous injection</td></tr>
<tr><td>Dosing</td><td><table>
<tr><th>Body weight (kg)</th><th>Dosing of reconstituted bulevirtide 2 mg powder for solution for injection (ml)</th><th>Bulevirtide Daily Dose</th></tr>
<tr><td>10 kg to <25 kg</td><td>0.5 ml</td><td>1 mg</td></tr>
<tr><td>25 kg to < 35 kg</td><td>0.75 ml</td><td>1.5 mg</td></tr>
<tr><td>35 kg and more</td><td>1 ml</td><td>2 mg</td></tr>
</table></td></tr>
<tr><td>Dosing in the health economic model (including relative dose intensity)</td><td>2 mg once daily

Mean exposure from baseline to w144 was [redacted]</td></tr>
</table>

Should the medicine be administered with other medicines?	According to the label, bulevirtide should be administered as monotherapy or in co-administration with a nucleoside or nucleotide analogue for treatment of underlying HBV infection.
Treatment duration / criteria for end of treatment	The optimal treatment duration is unknown. Treatment should be continued as long as associated with clinical benefit.
Necessary monitoring, both during administration and during the treatment period	Renal function should be carefully monitored.
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	None. Denmark already reflex-tests HBV infected individuals for co-infection with HDV.
Package size(s)	2 mg, 30 vials

Abbreviations: EMA = European Medicines Agency; HBV = hepatitis B virus; HDV = hepatitis delta virus; RDI = relative dose intensity

Bulevirtide blocks the entry of HBV and HDV into hepatocytes by binding to and inactivating NTCP (15). By blocking the essential entry receptor, the de novo infection of liver cells is decreased, viral spread is inhibited, and the life cycle of HDV is disrupted. A reduction in the number of infected cells ultimately protects uninfected and newly formed hepatocytes from new and re-infection (4, 52, 53).

In contrast to directly acting antivirals where viral production must be significantly reduced first to achieve biochemical remission, treatment with entry inhibitors reduces the plasma levels of HDV RNA, due to a decline in the number of infected, virus producing hepatocytes in the liver (53).

3.4.1 Description of ATMP

Not applicable for this application.

3.4.2 The intervention in relation to Danish clinical practice

As described in Section 3.3, off-label pegIFN-α is recommended as a possible treatment option for people with HBV coinfected with HDV by EASL, AASLD, and most importantly DSGH (41, 44, 45). Bulevirtide is expected to establish itself as the standard treatment for patients in fibrosis stages F2 or F3 who are ineligible for pegIFN-α or who have already attempted pegIFN-α treatment without effect, or for patients who are cirrhotic.

3.5 Choice of comparator(s)

Danish treatment guidelines clearly define that bulevirtide should be considered in patients who are cirrhotic, or in fibrosis stages F2 or F3 where pegIFN-α has not been effective or cannot be used (i.e. due to side-effects or contraindications). As such, in addition to pegIFN-α being off-label and non-recommended by DMC, pegIFN-α is an inappropriate comparator from a clinical perspective. No other treatment is indicated, or used, for the treatment of chronic hepatitis delta where pegIFN-α has not been effective or cannot be used (i.e. due to side-effects or contraindications). Conclusively, we consider no active treatment with best supportive care (BSC) (hereafter referenced to as BSC only) the appropriate comparator to bulevirtide in addition to BSC. Since HDV infection is dependent on the presence of HBV, treatment of HBV with nucleoside/nucleotide analogues (NAs) is recommended if there is significant fibrosis combined with either HBV DNA >2,000 IU/ml or ALT above the upper limit of normal (41). This is reflected in MYR301 where 61.3% of patients in the treatment and BSC arm combined received concomitant NA treatment for chronic HBV infection during the treatment period in accordance with the current EASL/AASLD treatment guidelines (35, 54). NAs have previously been found to be ineffective for the treatment of HDV infections and are not recommended for controlling CHD (45). Consequently, NA treatment should be considered as part of BSC, both for the comparator and the intervention. Accordingly, Table 4 is not applicable.

Table 4 Overview of comparator

Overview of comparator	
Generic name	N/A
ATC code	N/A
Mechanism of action	N/A
Method of administration	N/A
Dosing	N/A
Dosing in the health economic model (including relative dose intensity)	N/A
Should the medicine be administered with other medicines?	N/A
Treatment duration/ criteria for end of treatment	N/A
Need for diagnostics or other tests (i.e. companion diagnostics)	N/A
Package size(s)	N/A

Abbreviations: N/A = not applicable

3.6 Cost-effectiveness of the comparator(s)

The most appropriate comparator, BSC only, has not been evaluated by the DMC.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

The MYR301 trial is crucial in determining the efficacy of bulevirtide in the treatment of patients with CHD. The relevance of efficacy outcomes was assessed based on their influence on treatment results and their inclusion in the health economic model. Consequently, outcomes related to HDV RNA level and ALT normalisation were deemed relevant. Other study outcomes, detailed in Appendix B, were not included in the health economic evaluation and are thus excluded from Table 5.

Table 5 Efficacy outcome measures relevant for the application

	Time point*	Definition	How was the measure investigated/method of data collection
Percentage of Participants with Combined Response MYR301 (NCT03852719)	Week 48, Week 96, Week 144, Week 192 and Week 240	Combined response was defined as fulfilment of two conditions simultaneously: Undetectable (< lower limit of quantification (LLOQ, target not detected)) HDV RNA or decrease by ≥ 2 log10 IU/mL from baseline; and ALT normalisation.	HDV RNA was determined by quantitative PCR at each visit. Quantification of HDV RNA levels was performed with the RoboGene HDV RNA quantification kit, Version 2.0 (Roboscreen), which has an LLOQ of 50 IU/mL and a LOD of 6 IU/mL. ALT was analysed from blood samples by central laboratory using standard methods.
Percentage of Participants with Undetectable HDV RNA MYR301 (NCT03852719)	Week 48, Week 96, Week 144, Week 192 and Week 240	Undetectable HDV RNA at Week 48 means undetectable (< LLOQ, target not detected) HDV RNA at Week 48.	HDV RNA was determined by quantitative PCR at each visit. Quantification of HDV RNA levels was performed with the RoboGene HDV RNA quantification kit, Version 2.0 (Roboscreen), which has an LLOQ of 50 IU/mL and a lower LOD of 6 IU/mL.
Virologic response MYR301 (NCT03852719)	Week 48, Week 96, Week 144, Week 192 and Week 240	HDV RNA decrease by ≥ 2 log10 IU/mL from baseline or undetectable HDV RNA (< LLOQ, target not detected).	
Percentage of Participants with Alanine Aminotransferase (ALT) Normalisation	Week 48, Week 96, Week 144, Week 192	ALT normalisation was defined as an ALT value within the normal range, based on the central laboratories [Russian sites: ≤ 31 U/L for females and ≤ 41 U/L for males; all other sites:	ALT was analysed from blood samples by central laboratory using standard methods.

MYR301 (NCT03852719)	and Week 240	≤ 34 U/L for females and ≤ 49 U/L for males])	
Change From Baseline in Liver Stiffness MYR301 (NCT03852719)	Week 48, Week 96, Week 144, Week 192 and Week 240	Change in liver stiffness (measured by FibroScan) was defined as deviations from liver stiffness at baseline (in kPa).	Transient elastometry (FibroScan) was done at screening and during the study as indicated in schedule of events to assess liver fibrosis staging. The results were presented in kPa and documented in the eCRF.

Abbreviations: ALT = alanine aminotransferase; eCRF = electronic case report form; HDV = hepatitis delta virus; kPa = kilopascal; LLOQ = lower limit of quantification; LOD = limit of detection; PCR = polymerase chain reaction

Source: (35, 55)

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

Validity of outcomes

The validity of outcomes was evaluated to ensure the credibility and generalizability of the studies, ensuring the potential of evidence-based decision-making and avoiding misinterpretations. Based on Table 5, outcomes including a decrease in HDV RNA, normalisation of ALT, and change in liver stiffness were validated.

HDV RNA and normalisation of ALT

According to the Food and Drug Administration (FDA), an appropriate surrogate endpoint for the treatment of HDV should provide evidence of both a decline in virologic replication and an improvement in associated liver inflammation as evident by biochemical response (56). Accordingly, the proportion of trial patients with undetectable serum HDV RNA (defined as less than lower limit of quantification [LLOQ] or target not detected) and ALT normalisation are considered fitting outcomes to predict clinical benefit (56). This is further supported by study data which suggests that a 2-log10 decline in HDV RNA is associated with clinical benefit, and data from Kamal *et al*. showing that patients with normal ALT level and HDV RNA undetectability have a significantly lower risk of experiencing progression to cirrhosis and experiencing liver related events (18, 57, 58). Guidance from the AASLD and EASL supports this approach. In the 2022 treatment endpoint conference report, experts recommended using HDV RNA below the LLOQ as an endpoint when HBsAg loss is rare, which is the case for MYR301, for finite strategies whereas the preferred endpoint of a maintenance strategy is HDV RNA below the LLOQ at 48 weeks on-treatment. Combined response is hereby described as an alternate endpoint option (59). The minimal clinically important difference (MCID) for HDV RNA is defined as either a ≥2.0 $\log_{10}$ IU/mL decline from baseline or undetectable levels below the LLOQ. For ALT, the MCID is defined as normalisation to within the laboratory reference range (≤ upper limit of normal [ULN]) (56, 59, 60).

Change in liver stiffness

The FDA recommends that change in liver stiffness should be considered as a secondary endpoint in trials investigating treatments for CHD (56). Liver stiffness rises with the accumulation of fibrotic extracellular matrix (mainly collagen), which means reductions in liver stiffness can reflect fibrosis regression (9, 61). Furthermore, liver stiffness measurements were considered a useful tool to determine patients at risk for cirrhosis in patients with CHD (62). The potential of testing liver stiffness as a marker for disease progression was further acknowledged by the EASL, suggesting yearly liver stiffness determination during and after antiviral treatment (45). No clear consensus exists about the MCID for the change of liver stiffness, however a change of approximately 2 kPa from baseline can be considered representative (63).

4. Health economic analysis

The developed health economic model aims to evaluate the cost-effectiveness of bulevirtide with BSC for the treatment of CHD, compared with the current management without bulevirtide in in F2-F3 patients where pegIFN-α has not been effective or cannot be used (i.e. due to side-effects or contraindications) or in patients with cirrhosis (F4), i.e. no active treatment with BSC for CHD (see Section 3.5 for more details regarding the choice of comparator).

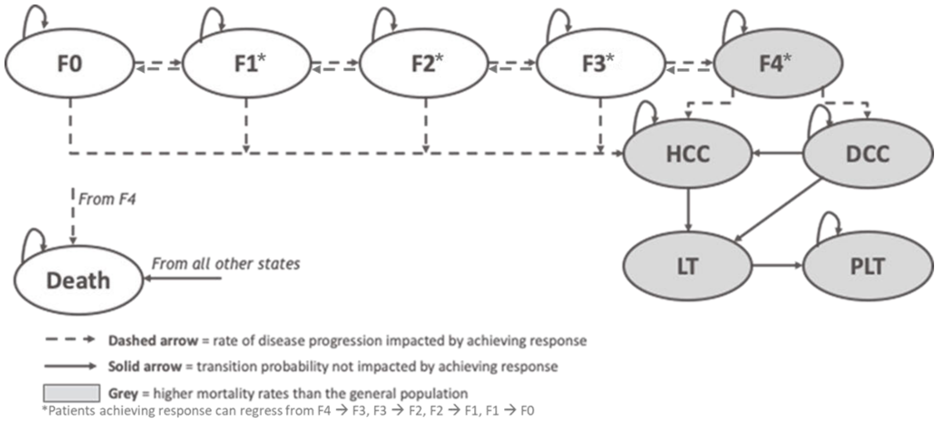
Costs and health outcomes, over a lifetime perspective are calculated for each treatment strategy.

4.1 Model structure

The model is structured as a decision tree followed by a Markov cohort model following patients through the lifetime of their disease. The Markov part of the model is based on state transition models, similar to other viral hepatitis models (64, 65). The model uses a 24-week cycle length and half cycle correction is applied to both costs and outcomes. At baseline, patients are distributed across fibrosis stages (43) and are assigned to treatment with bulevirtide complemented with BSC or BSC only (see Section 3.5). In the decision tree part of the model, patient response is evaluated. Patients can be evaluated to only exhibit a virologic response defined as HDV-RNA undetectability or decrease by ≥2 log10 from baseline, or a complete response defined as reaching the combined endpoint from MYR301, i.e. HDV-RNA undetectability or 2log decline as well as ALT normalisation (Section 3.7.1), or non-responders not reaching any of the defined outcomes. The evaluation is made at week 48 and week 96 of treatment. At the evaluation patients that are not considered to be responders are affected by the treatment stopping rule and taken off treatment. In the base case, patients who did not reach the combined endpoints at week 96 are considered non-responders and are taken off treatment. At weeks 144, 196, and 240 patients that have reached and sustained undetectable HDV-RNA levels for at least 96 weeks are taken off treatment. A proportion of these patients are assumed to relapse to detectable HDV-RNA levels after discontinuing treatment and therefore resumes active treatment. Stopping rules are further described in Section 8.4.

All patients (regardless of response) progress through liver disease, from F0 (no fibrosis) to F3 (bridging fibrosis), before developing cirrhosis, i.e. fibrosis stage 4. Cirrhotic patients can maintain limited symptoms, i.e. compensated cirrhosis, before developing decompensated cirrhosis (DCC). As the chronic disease progresses, the risk of developing HCC increases. Over the course of a simulation process, patients can achieve spontaneous or a treatment-induced response (e.g., HbsAg seroconversion or HDV combined response endpoint) or develop liver complications (e.g., CC, DCC, HCC, or LT). Note that the population relevant for assessment is limited to patients in fibrosis stages F2, F3, and F4 at the time of treatment initiation (Section 3.2).

Figure 1 Model structure overview



Abbreviations: F0: fibrosis stage 0; F1: fibrosis stage 1; F2: fibrosis stage 2; F3: fibrosis stage 3; F4: fibrosis stage 4; CC: compensated cirrhosis; DCC: decompensated cirrhosis; HCC: hepatocellular carcinoma; LT: liver transplant; PLT: post-liver transplant

The model links the efficacy of treatments to the slowing of disease progression using the combined response endpoint. This is based on the assumption that improvement in both virologic and inflammation biomarkers slows disease progression (see Section 3.7.1, Validity of Outcomes). Reduced disease progression is incorporated into the model results via a reduction in HDV-related morbidity, mortality, healthcare resource utilisation (HCRU), costs and improvement in patient quality of life. Health state transitions for both responders and non-responders are illustrated above in Figure 1. Responders can progress or regress through stages F0-F4 while on treatment; non-responders can only progress through F0-F4. From all fibrosis stages, all patients can develop HCC (39). Moreover, from CC (fibrosis stage 4 [F4]), all patients can develop HCC or DCC. From the DCC state, patients may move to the HCC state or undergo a LT. In the LT state, patients only remain for one cycle and then either move to PLT or death. For all advanced health states (i.e. CC, DCC, HCC, LT and PLT), increased mortality rates are assumed (see Section 8.1.2). While transitions for responders and non-responders are similar, responder patients progress slower than non-responders (detailed by disease progression hazard ratios in Table 18). As noted above, responders can also regress through stages F0-F4. The possibility to regress was previously described by Farci, Roskams (18) and was further confirmed by a clinical expert (39). Moreover, fibrosis regression was observed in HBV mono-infected patients who are virologically supressed on HBV-treatment (66) which could be considered a relevant proxy for HDV patients achieving combined response (39). Age-specific background mortality rates are applied to the model's entire population regardless of health state. The background mortality is sourced from the Danish Medicines Council (67).

4.2 Model features

Features of the economic model are summarised in Table 6.

Table 6 Features of the economic model

Model features	Description	Justification
Patient population	Plasma (or serum) HDV-RNA positive adults and paediatric patients 3 years of age and older weighing at least 10 kg with compensated liver disease and fibrosis stage F2 to F4 that are ineligible for pegIFN-α or who have already attempted pegIFN-α treatment.	In line with patient population described in Section 3.2.
Baseline health state distribution	[redacted]	Data on file [redacted]
Perspective	Limited societal perspective	According to DMC guidelines.
Time horizon	64 years	To capture all health benefits and costs in line with DMC guidelines.
Cycle length	24 weeks	Consistent with responder criteria.
Half-cycle correction	Yes	Applied to cost and outcomes.
Discount rate	3.5 %	According to DMC guidance
Intervention	Bulevirtide with BSC	Aligned with the trial and expected clinical practice. BSC includes treatment for underlying HBV.
Comparator(s)	No active treatment with BSC	There is currently no approved treatment for the patient population.
Outcomes	Composite endpoint, virological response, LYs, QALYs, costs, and ICER	Used to evaluate response status, cost and benefits of the intervention.

Abbreviations: DMC = Danish Medicines Council; F2/3/4 = fibrosis stage 2/3/4; HDV = hepatitis delta virus; ICER = incremental cost-effectiveness ratio; LYs = life years; QALYs = quality-adjusted life years

5. Overview of literature

5.1 Literature used for the clinical assessment

The present application contains clinical evidence (efficacy and safety) based on the pivotal Phase III clinical trial for the efficacy and safety of bulevirtide, MYR301, which directly compared the efficacy of bulevirtide at 2 mg to delayed treatment/BSC (55). A systematic literature review (SLR), summarised below, was conducted to ensure an exhaustive review of relevant literature and to increase understanding of the treatment of CHD. No other trials than MYR301 with the relevant comparator was identified. The relevant publications used for the clinical assessment are listed in Table 7 (69, 70). The SLR is summarized in Appendix H.

Table 7 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
Wedemeyer H, Aleman S, Brunetto MR, Blank A, Andreone P, Bogomolov P et al.; MYR 301 Study Group. A Phase 3, Randomized Trial of Bulevirtide in Chronic Hepatitis D. N Engl J Med. 2023 Jul 6;389(1):22-32. doi: 10.1056/NEJMoa2213429. Epub 2023 Jun 22. Wedemeyer, Aleman (69) Wedemeyer H, Aleman S, Brunetto M, Blank A, Andreone P, Bogomolov P et al. Bulevirtide monotherapy in patients with chronic HDV: Efficacy and safety results through week 96 from a phase III randomized trial. J Hepatol. 2024 Oct;81(4):621-629. doi: 10.1016/j.jhep.2024.05.001. Epub 2024 May 9. Wedemeyer, Aleman (70)	MYR301	NCT03852719	Start: 17/04/19 Completion: 08/08/24 Data cut-off 26/11/20	Bulevirtide 2 mg and bulevirtide 10 mg vs. delayed treatment/BSC for 48 weeks for patients with chronic hepatitis D.
Data on file Unpublished data 2025: MYR301 Clinical Study Report (35)	MYR301	NCT03852719	Start: 17/04/19 Completion: 08/08/24 Data cut-off 08/08/24	Bulevirtide 2 mg and bulevirtide 10 mg vs. delayed treatment/BSC up to 240 weeks for patients with chronic hepatitis D.
Data on file Unpublished data 2023: MYR301 Clinical study protocol and statistical analysis plan (54)	MYR301	NCT03852719	Start: 17/04/19 Completion: 08/08/24 Data cut-off 08/08/24	Bulevirtide 2 mg and bulevirtide 10 mg vs. delayed treatment/BSC up to 240 weeks for patients with chronic hepatitis D.

Sources: (35, 69)

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

To supplement the global model with utilities for the severe liver disease health states data relevant to the Danish setting, a targeted literature review (TLR) was performed. The TLR resulted in the finding of Kaushik et al. (71), a SLR and meta-analysis of utility values for Hepatitis B, C, and D. The SLR done in Kaushik et al. (71) found 24 studies relevant for the meta-analysis. For this submission 2 of these studies were found to be appropriate for conversion of the UK tariffs index scores to Danish index scores as described in Section 10.3. These values used in the model stem from a SLR and meta-analysis and hence no SLR for health-related quality of life was conducted for this application, leaving Appendix I blank.

Table 8 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
Kaushik A, Kim CH, Hofmann S, Janeiro MJ, Lloyd A, Aragão F. A Systematic Literature Review and Meta-Analysis of Primary Evidence Reporting Health-State Preference Values in Chronic Hepatitis B, C, and D. Value Health. 2024 Dec;27(12):1779-1788. doi: 10.1016/j.jval.2024.06.002. Epub 2024 Jun 19. Kaushik et al. (71)	Utility values for severe liver disease health states	Section 10.3
Scalone L, Ciampichini R, Fagiuoli S, Gardini I, Fusco F, Gaeta L, Del Prete A, Cesana G, Mantovani LG. Comparing the performance of the standard EQ-5D 3L with the new version EQ-5D 5L in patients with chronic hepatic diseases. Qual Life Res. 2013 Sep;22(7):1707-16. doi: 10.1007/s11136-012-0318-0. Epub 2012 Nov 29. PMID: 23192232. Scalone et al.(72)	Utility values for severe liver disease health states	Section 10.3
Björnsson E, Verbaan H, Oksanen A, Frydén A, Johansson J, Friberg S, Dalgård O, Kalaitzakis E. Health-related quality of life in patients with different stages of liver disease induced by hepatitis C. Scand J Gastroenterol. 2009;44(7):878-87. doi: 10.1080/00365520902898135. PMID: 19437190. Björnsson et al. (73)	Utility values for severe liver disease health states	Section 10.3

Buti M, Wedemeyer H, Aleman S, Chulanov V, Morozov V, Sagalova O, Stepanova T, Gish RG, Lloyd A, Kaushik AM, Suri V, Manuilov D, Osinusi AO, Flaherty JF, Lampertico P. Patient-reported outcomes in chronic hepatitis delta: An exploratory analysis of the phase III MYR301 trial of bulevirtide. J Hepatol. 2025 Jan;82(1):28-36. doi: 10.1016/j.jhep.2024.06.031. Epub 2024 Jul 14. Buti et al. (74)	EQ-5D-3L	Section 10
Hvidberg MF, Petersen KD, Davidsen M, Witt Udsen F, Frølich A, Ehlers L, Alava MH. Catalog of EQ-5D-3L Health-Related Quality-of-Life Scores for 199 Chronic Conditions and Health Risks in Denmark. MDM Policy Pract. 2023 Apr 9;8(1):23814683231159023. doi: 10.1177/23814683231159023. Hvidberg et al. (75)	Disutilities for fatigue, thrombocytopenia, neutropenia, leukopenia, and anaemia	Section 10.3
Torkilseng EB, Clarke N, Sopina L, Oddershede L, Wolf RT, Lawrance R, Trigg A, Bennett B, Shaw JW. Predicting Danish EQ-5D-5L Utilities Based on United Kingdom EQ-5D-3L Utilities for Use in Health Economic Models. Pharmacoecon Open. 2025 May;9(3):433-443. doi: 10.1007/s41669-025-00562-6. Epub 2025 Feb 22. Torkilseng et al. (76)	DK EQ-5D-5L	Section 10.2

5.3 Literature used for inputs for the health economic model

In order to adapt the health economic model to the Danish setting with relevant inputs and to incorporate the application with the newest available evidence of the clinical effect of bulevirtide, a pragmatic TLR was performed to supplement the SLR presented in Appendix J. The resulting publications included are listed in Table 9.

Table 9 Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimat e	Method of identification	Reference to where in the application the data is described/applied

Alfaiate D, Clément S, Gomes D, Goossens N, Negro F. Chronic hepatitis D and hepatocellular carcinoma: A systematic review and meta-analysis of observational studies. J Hepatol. 2020 Sep;73(3):533-539. doi: 10.1016/j.jhep.2020.02.030. Epub 2020 Mar 6. Alfaiate et al. (24)	Disease transition rate	Desk research	Section 8.1.2
Asphaug L, Thiele M, Krag A, Melberg HO. Cost-Effectiveness of Noninvasive Screening for Alcohol-Related Liver Fibrosis. Hepatology. 2020 Jun;71(6):2093-2104. Asphaug et al. (77)	Cost for treatment of CC	Desk research	Section 11.4
Bermingham SL, Hughes R, Fenu E, Sawyer LM, Boxall E, T Kennedy P, Dusheiko G, Hill-Cawthorne G, Thomas H. Cost-Effectiveness Analysis of Alternative Antiviral Strategies for the Treatment of HBeAg-Positive and HBeAg-Negative Chronic Hepatitis B in the United Kingdom. Value Health. 2015 Sep;18(6):800-9. doi: 10.1016/j.jval.2015.05.007. Epub 2015 Jul 27. Bermingham et al. (65)	Disease transition rate	Desk research	Section 8.1.2
Da BL, Heller T, Koh C. Hepatitis D infection: from initial discovery to current investigational therapies. Gastroenterol Rep (Oxf). 2019 Jun 23;7(4):231-245. doi: 10.1093/gastro/goz023. Da et al. (17)	Disease transition rate	Desk research	Section 8.1.2
Dakin H, Bentley A, Dusheiko G. Cost-utility analysis of tenofovir disoproxil fumarate in the treatment of chronic hepatitis B. Value Health. 2010 Dec;13(8):922-33. doi: 10.1111/j.1524-4733.2010.00782.x. Epub 2010 Sep 3. Dakin et al. (78)	Disease transition rate	Desk research	Section 8.1.2
Data on file Unpublished data 2025: MYR301 Clinical Study Report Data on file (35)	HDV RNA and ALT related endpoints	Primary clinical trial study for the intervention	Section 6 and Appendix B

Fattovich G, Giustina G, Christensen E, Pantalena M, Zagni I, Realdi G, Schalm SW. Influence of hepatitis delta virus infection on morbidity and mortality in compensated cirrhosis type B. The European Concerted Action on Viral Hepatitis (Eurohep). Gut. 2000 Mar;46(3):420-6. doi: 10.1136/gut.46.3.420. Fattovich et al. (3)	Disease transition rate	Desk research	Section 8.1.2
Fattovich G. Natural history and prognosis of hepatitis B. Semin Liver Dis. 2003 Feb;23(1):47-58. doi: 10.1055/s-2003-37590. Fattovich (79)	Disease transition rate	Desk research	Section 8.1.2
Hsu YS, Chien RN, Yeh CT, Sheen IS, Chiou HY, Chu CM, Liaw YF. Long-term outcome after spontaneous HBeAg seroconversion in patients with chronic hepatitis B. Hepatology. 2002 Jun;35(6):1522-7. doi: 10.1053/jhep.2002.33638. Hsu et al. (80)	Disease transition rate	Desk research	Section 8.1.2
Jepsen P, Ott P, Andersen PK, Sørensen HT, Vilstrup H. Clinical course of alcoholic liver cirrhosis: a Danish population-based cohort study. Hepatology. 2010 May;51(5):1675-82. Jepsen et al. (81)	Proportion of patients with complications due to DCC.	Desk research	Section 11.4
Lidgren M, Hollander A, Weiland O, Jönsson B. Productivity improvements in hepatitis C treatment: impact on efficacy, cost, cost-effectiveness and quality of life. Scand J Gastroenterol. 2007 Jul;42(7):867-77. Lidgren et al. (82)	Cost of post-liver transplantation	Desk research	Section 11.4
Sullivan PW, Ghushchyan V. Preference-Based EQ-5D index scores for chronic conditions in the United States. Med Decis Making. 2006 Jul-Aug;26(4):410-20. Sullivan and Ghushchyan (83)	Disutilities	Desk research	Section 10.3

Wedemeyer H, Aleman S, Brunetto MR, Blank A, Andreone P, Bogomolov P, Chulanov V, Mamonova N, Geyvandova N, Morozov V, Sagalova O, Stepanova T, Berger A, Manuilov D, Suri V, An Q, Da B, Flaherty J, Osinusi A, Liu Y, Merle U, Schulze Zur Wiesch J, Zeuzem S, Ciesek S, Cornberg M, Lampertico P; MYR 301 Study Group. A Phase 3, Randomized Trial of Bulevirtide in Chronic Hepatitis D. N Engl J Med. 2023 Jul 6;389(1):22-32. Wedemeyer et al. (69)	HDV RNA and ALT related endpoints	Primary clinical trial study for the intervention / SLR	Section 6 and Appendix B
Wedemeyer H, Aleman S, Brunetto M, Blank A, Andreone P, Bogomolov P, et al. (2024). Bulevirtide monotherapy in patients with chronic HDV: Efficacy and Safety Results Through Week 96 from a Phase III Randomized Trial. J Hepatol. 2024; 81(4): 621-629. Wedemeyer et al. (70)	HDV RNA and ALT related endpoints	Primary clinical trial study for the intervention / SLR	Section 6 and Appendix B

Abbreviation: ALT = alanine aminotransferase; CC = compensated cirrhosis; DCC = decompensated cirrhosis; HDV = hepatitis delta virus

6. Efficacy

6.1 Efficacy of bulevirtide compared to best supportive care for treatment of patients with chronic hepatitis delta

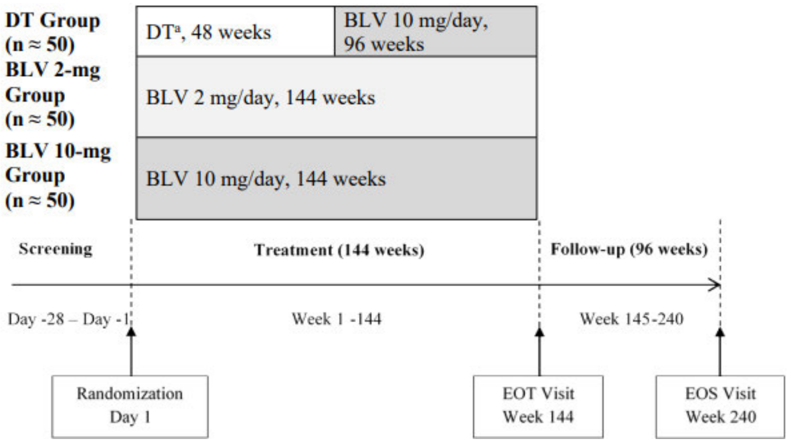
6.1.1 Relevant studies

6.1.1.1 MYR301 (NCT03852719)

The MYR301 study was a multicentre, open-label, randomized Phase 3 clinical study and designed to assess the efficacy and safety of bulevirtide treatment (2 mg/d and 10 mg/d) in people with CHD, in comparison to delayed treatment (no treatment for 48 weeks, followed by bulevirtide 10mg/d for 96 weeks). The influence of bulevirtide on quality of life was also assessed (35, 69). The study design (Figure 2), study duration and PICO criteria are summarised in Table 10.

Further information is available in Appendix B.

Figure 2 MYR301 study design



Abbreviations: BLV = bulevirtide; DT = delayed treatment; EOS = end of study; EOT = end of treatment; HDV = hepatitis delta virus

[a] DT meant no treatment for HDV infection for 48 weeks.

Source: (35)

Table 10 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
A Multicenter, Open-label, Randomized Phase 3 Clinical Study to Assess Efficacy and Safety of Bulevirtide in Patients with Chronic Hepatitis Delta (MYR301), NCT03852719 (35, 69, 70, 74)	Multicenter, open-label, randomized Phase 3 clinical study of bulevirtide vs. delayed treatment/BSC	The total study duration is 240 weeks. The delayed treatment arm received no treatment for 48 weeks and thereafter bulevirtide 10 mg for 96 weeks. The bulevirtide 2 mg and 10 mg arms received treatment for 144 weeks. All arms were followed off treatment for another 96 weeks.	Treatment of adult patients with chronic hepatitis delta	Bulevirtide 2 mg or bulevirtide 10 mg once daily	Best supportive care for the first 48 weeks, thereafter bulevirtide 10 mg	Combined response (2log decline or undetectable HDV RNA and ALT normalisation; 48 weeks, follow-up to 240 weeks, predefined in exploratory efficacy outcomes), ALT normalisation (48 weeks, follow-up to 240 weeks, predefined in exploratory efficacy outcomes), Undetectable HDV RNA (48 weeks, follow-up to 240 weeks, predefined in exploratory outcomes), Change from baseline in liver stiffness (48 weeks, follow-up to 240 weeks, predefined), Proportion of participants with HDV RNA decrease by ≥ 2 log10 IU/mL or undetectable HDV RNA (48 weeks, follow-up to 240 weeks, predefined in exploratory outcomes).

Abbreviations: ALT = alanine aminotransferase; BSC = best supportive care; HDV = hepatitis delta virus

6.1.2 Comparability of studies

Not applicable, the comparison is based on the head-to-head study MYR301.

6.1.2.1 Comparability of patients across studies

Not applicable, the comparison is based on the head-to-head study MYR301.

Table 11 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	[Study name]		[Study name]		[Study name]	
	[int./ comp.]	[int./ comp.]	[int./ comp.]	[int./ comp.]	[int./ comp.]	[int./ comp.]
Age						
Gender						
[characteristic]						

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

The economic analysis utilises patient characteristics informed by Kamal, Westman (38) and confirmed by a clinical expert (Table 12) (39).

Table 12 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (38, 39)	Value used in health economic model
Age, years	36.3	36.3
Gender, male sex (%)	51.1	51.1

6.1.4 Efficacy – results per MYR301

A summary of outcomes from the MYR301 trial is shown in Table 13. Because patients in the comparator arm received bulevirtide 10 mg after Week 48, data and comparisons for BSC are limited to Week 48. The full analysis set (FAS) was the primary analysis set for efficacy analyses. More details about the respective outcomes are described in Appendix B.

Table 13 Summary of outcomes from the MYR301 trial

Outcome	Chosen population	Bulevirtide 2 mg (N=49)	BSC[a] (N=51)	Response rate diff vs BSC, %	p-value

Participants with Combined Response, n (%) (top to bottom: Week 48, Week 96, Week 144, Week 192 and Week 240)	FAS	22 (44.9)	1 (2)	42.9 (96% CI 27, 58.5)	< 0.0001
		27 (55.1)	N/A	N/A	N/A
		28 (57.1)	N/A	N/A	N/A
		11 (22.4)	N/A	N/A	N/A
		12 (24.5)	N/A	N/A	N/A
Participants with Undetectable HDV RNA, n (%) (top to bottom: Week 48, Week 96, Week 144, Week 192 and Week 240)	FAS	6 (12.2)	0	12.2 (2.89, 21.51)[b]	0.0102[b]
		10 (20.4)	N/A	N/A	N/A
		14 (28.6)	N/A	N/A	N/A
		8 (16.3)	N/A	N/A	N/A
		10 (20.4)	N/A	N/A	N/A
Participants with ALT Normalisation, n (%) (top to bottom: Week 48, Week 96,	FAS	25 (51)	6 (11.8)	39.3 (95% CI 20, 55.8)	< 0.0001
		31 (63.3)	N/A	N/A	N/A

Week 144, Week 192 and Week 240)		29 (59.2)	N/A	N/A	N/A
		13 (26.5)	N/A	N/A	N/A
		12 (24.5)	N/A	N/A	N/A
Change from baseline in liver stiffness as measured by elastography, LS-mean kPa (top to bottom: Week 48, Week 96, Week 144, Week 192 and Week 240)	FAS	-3.38	0.87	-3.93 (95% CI -6.23, -1.63)	0.0009
		-4.31	N/A	N/A	N/A
		-5.24	N/A	N/A	N/A
		-3.74	N/A	N/A	N/A
		-1.2	N/A	N/A	N/A
HDV RNA Decrease by ≥ 2 log10 IU/mL From Baseline or Undetectable HDV RNA (Virologic Response), n (%)	FAS	36 (73.5)	2 (3.9)	69.5 (95% CI 54.1, 81.9)	< 0.0001
		37 (75.5)	N/A	N/A	N/A

(top to bottom: Week 48, Week 96, Week 144, Week 192 and Week 240)	36 (73.5)	N/A	N/A	N/A
	14 (28.6)	N/A	N/A	N/A
	16 (32.7)	N/A	N/A	N/A

Note: Combined response defined as undetectable HDV RNA (< LLOQ, target not detected) or HDV RNA decreased ≥ 2 log10 IU/mL from baseline combined with ALT normalisation.

[a] From Week 48 through the end of treatment, participants received bulevirtide 10 mg.

[b] The comparison between the bulevirtide 2 mg arm and the BSC arm was not included in formal testing.

Abbreviations: ALT = alanine aminotransferase; BSC = best supportive care; FAS = full analysis set; HDV = hepatitis delta virus; kPa = kilopascal; LS = least square; N/A = not applicable; NR = not reported

Source: (35, 69, 70)

7. Comparative analyses of efficacy

Not applicable.

7.1.1 Differences in definitions of outcomes between studies

7.1.2 Method of synthesis

7.1.3 Results from the comparative analysis

Results from the comparative analysis of the head-to-head study MYR301 are depicted in Table 14.

Table 14 Results from the comparative analysis of bulevirtide 2 mg vs. BSC for patients with chronic hepatitis D

Outcome measure	Bulevirtide (N=49)	BSC (N=51)	Result
Participants With Combined Response at Week 48, n (%; CI [%])	22 (44.9; 30.7, 59.8)	1 (2; 0, 10.4)	RRD: 21 (42.9; 27, 58.5)
Participants With Undetectable HDV RNA at Week 48, n (%; CI [%])	6 (12.2; 4.6, 24.8)	0 (0; 0, 7)	RRD: 6 (12.2; 2.89, 21.51[a])

Participants With ALT Normalisation at Week 48, n (%; CI [%])	25 (51; 36.3, 65.6)	6 (11.8; 4.4, 23.9)	RRD: 19 (39.3; 20, 55.8)
Change from baseline in liver stiffness as measured by elastography at Week 48, LS-mean kPa (95% CI)	-3.06 (-4.67, -1.45) SE of LS-mean: 0.814	0.87 (-0.79, 2.53) SE of LS-mean: 0.839	LS-mean of difference: -3.93 (-6.23, -1.63) SE of LS-mean of difference: 1.162
HDV RNA Decrease by ≥ 2 log10 IU/mL From Baseline or Undetectable HDV RNA (Virologic Response) at Week 48, n (%; CI [%])	36 (73.5; 58.9, 85.1)	2 (3.9; 0.5, 13.5)	RRD: 34 (69.5; 54.1, 81.9)

Note: Combined response defined as undetectable HDV RNA (< LLOQ, target not detected) or HDV RNA decreased ≥ 2 log10 IU/mL from baseline combined with ALT normalisation. Source: (35)

[a] The comparison between the bulevirtide 2 mg arm and the BSC arm was not included in formal testing

Abbreviations: ALT = alanine aminotransferase; BSC = best supportive care; HDV = hepatitis delta virus; kPa = kilopascal; LS = least square; NR = not reported; RRD = response rate difference; SE = standard error

7.1.4 Efficacy – results per [outcome measure]

Not applicable

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

Not applicable.

8.1.1.1 Extrapolation of [effect measure 1]

Not applicable.

Table 15 Summary of assumptions associated with extrapolation of [effect measure]

Method/approach	Description/assumption
Data input	[Name of registrational study, name of studies from indirect comparison]
Model	[Describe which/how many models have been applied in extrapolating efficacy e.g. full parametrization vs. piecewise]

Assumption of proportional hazards between intervention and comparator	[Yes/No/Not applicable]
Function with best AIC fit	[Intervention: X function] [Comparator: X function]
Function with best BIC fit	[Intervention: X function] [Comparator: X function]
Function with best visual fit	[Intervention: X function] [Comparator: X function]
Function with best fit according to evaluation of smoothed hazard assumptions	[Intervention: X function] [Comparator: X function]
Validation of selected extrapolated curves (external evidence)	[E.g. studies, databases, RWE, clinical experts' opinions on clinical plausibility]
Function with the best fit according to external evidence	[Intervention: X function] [Comparator: X function]
Selected parametric function in base case analysis	[Intervention: X function] [Comparator: X function]
Adjustment of background mortality with data from Statistics Denmark	[Yes/No] If 'No': briefly describe why the data has not been adjusted for background mortality
Adjustment for treatment switching/cross-over	[Yes/No] If 'Yes': briefly describe the assumption/method
Assumptions of waning effect	[Yes/No] If 'Yes': briefly describe the assumption/method
Assumptions of cure point	[Yes/No] If 'Yes': briefly describe the assumption/method

8.1.1.2 Extrapolation of [effect measure 2]

Not applicable.

8.1.2 Calculation of transition probabilities

The model differentiates between responders and non-responders, where response is defined as reaching the combined endpoint, i.e. HDV-RNA undetectability or 2log decline as well as ALT normalisation. Transition probabilities (TPs) for non-responders are based on the natural history of HDV, and the TPs for responders are based on HRs of progression applied to the transitions of the non-responders resulting in a slower disease progression. TPs are calculated in the following steps:

Step 1: TPs for non-responders are based on the natural history of HDV and are derived from the literature (Table 16). Further details are described in Section 8.1.2.1.

Step 2: TPs were validated using external data as described in Section 8.1.2.2.

Step 3 TPs for responders includes a reduced pace in disease progression compared to the natural history of HDV. The reduced pace in disease progression is calculated by applying published HR of treated vs. untreated patients, further supported by study results of sub-group analyses within treated patients (58), described in Sections 8.1.2.3.1 and 8.1.2.3.2. The HRs of disease progression in responders versus non-responders are applied on natural history transitions rates from which responder-specific transition probabilities are calculated, as described in Section 8.1.2.3.3. The TPs for responders are shown in Table 19.

Transitions for responders also include potential fibrosis regression which are described in Section 8.1.2.3.3. The responders in the model, as shown in Section 4.1, are able to regress from stage F4 to F0 incrementally. The possibility to regress was previously described by Farci, Roskams (18) and was further confirmed by a clinical expert (39). Moreover, fibrosis regression was observed in HBV mono-infected patients who are virologically supressed on HBV-treatment (66) which could be considered a relevant proxy for HDV patients achieving combined response (39).

8.1.2.1 Transition probabilities for non-responders (step 1)

For patients who are non-responders, disease progression is modelled through the natural history of HDV infection. A targeted literature search was performed to identify natural history data in HDV which identified multiple publications that were heterogenous both in terms of duration and geographic focus. The population sizes (n) of the identified studies were generally small, reflecting the orphan nature of the disease. Given the data limitations and heterogeneity in study designs, it was decided to calculate the natural history of HDV progression based on publications comparing disease progression in HDV/HBV co-infected individuals versus HBV mono-infected patients. This is reflective of the decision problem being modelled in the present health economic evaluation. The approach was validated with experts, given the more robust data in HBV mono-infection and the well-established relationship of accelerated progression in HDV/HBV co-infected versus HBV mono-infected patients (see Section 3.1).

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Table 16 shows the relationship between HBV annual TP and HDV annual TP. TPs from HBV were first converted to annual rates using the following relationship (probability = 1 – EXP (-rate * time)). Then the annual rates were scaled by ratios from publication to determine the annual HDV rates. Finally, the HDV rates was transformed back into annual TPs for HDV. These were used in the model and can be found in the NAT_HIS sheet in the model.

Table 16 Relationship between HBV annual TPs and HDV annual TPs

Health state (from)	Health state (to)	HBV Annual TP	HBV Annual Rate	HDV vs HBV Odds Ratio	HDV Annual Rate	HDV Annual TP	Source HBV TP	Source HDV OR
Fx	Fx+1	5.30%	0.0545	3.0	0.1634	15.07%	Bermingham et al. (65) [sourced from Fattovich G. Natural history of hepatitis B. J Hepatol 2003;39(Suppl. 1): S50–8.] (17)	Based on a literature review, Da et al. (17) reported a 2 to 3-fold relative risk for patients with Hepatitis D (Table 3 in Da et al. (17)). A 3-fold relative risk increase was assumed as this fits best with the natural history data from Romeo, Del Ninno (21).
	HCC	0.50%	0.0050	2.77	0.0139	1.38%	Bermingham et al. (65) [sourced from Chen CJ, Iloeje UH, Yang HI. Long-term outcomes in hepatitis B: the REVEAL HBV study. Clin Liver Dis 2007;11:797–816] & (3)	Based on a meta-analysis, Alfaiate et al. (24) reported a significantly higher risk of HCC in patients with Hepatitis D: a pooled odds ratio of 2.77 (Figure 2B in Alfaiate et al. (24)).
CC (F4)	DCC	5.00%	0.0513	2.2	0.1128	10.67%	Bermingham et al. (65) [sourced from Dakin H, Bentley A, Dusheiko G. Cost-utility analysis of tenofovir disoproxil fumarate in the treatment of chronic hepatitis B. Value Health 2010;13:922–33.] (3)	Based on a retrospective cohort study. Fattovich et al. (3) reported that the risk for decompensation, after adjustment for clinical and serological differences at baseline, was increased by a factor of 2.2 in anti-HDV positive relative to HDV negative cirrhotic patients (Table 5 in Fattovich et al. (3)).
	HCC	2.30%	0.0233	2.77	0.0645	6.24%	Bermingham et al. (65) [sourced from Dakin H, Bentley A, Dusheiko G. Cost-utility analysis of tenofovir disoproxil fumarate in the treatment of chronic hepatitis B. Value Health 2010;13:922–33.] (24)	Based on a meta-analysis, Alfaiate et al. (24) reported a significantly higher risk of HCC in patients with Hepatitis D: a pooled odds ratio of 2.77 (Figure 2B in Alfaiate et al. (24)).

	Death	3.70%	0.0377	2.0	0.0754	7.26%	Bermingham et al. (65) [sourced from Fattovich G. Natural history and prognosis of hepatitis B. Semin Liver Dis 2003;23:47–58.] (24)	Based on a retrospective cohort study. Fattovich et al. (3) reported that the mortality risk, after adjustment for clinical and serological differences at baseline, was increased by a factor of 2.0 in anti-HDV positive relative to HDV negative cirrhotic patients (Table 5 in Fattovich et al. (3)).
DCC	HCC	2.90%	0.0294	2.77	0.0815	7.83%	Bermingham et al. (65) [sourced from Dakin H, Bentley A, Dusheiko G. Cost-utility analysis of tenofovir disoproxil fumarate in the treatment of chronic hepatitis B. Value Health 2010;13:922–33.]	Based on a meta-analysis, Alfaiate et al. (24) reported a significantly higher risk of HCC in patients with Hepatitis D: a pooled odds ratio of 2.77 (Figure 2B in Alfaiate et al. (24)).
	LT					1.55%	Bermingham et al. (65) [sourced from NHS Blood and Transplant. Transplant Activity in the UK. Bristol, UK: NHS Blood and Transplant, 2010]	
	Death					15.60%	Bermingham et al. (65) [sourced from Fattovich G. Natural history and prognosis of hepatitis B. Semin Liver Dis 2003;23:47–58.] & Alfaiate et al. (24)	
HCC	LT					1.55%	Bermingham et al. (65) [sourced from Dakin H, Bentley A, Dusheiko G. Cost-utility analysis of tenofovir disoproxil fumarate in the treatment of chronic hepatitis B. Value Health 2010;13:922–33.]	
	Death					56.00%	Bermingham et al. (65) [sourced from Dakin H, Bentley A, Dusheiko G. Cost-utility analysis of tenofovir disoproxil fumarate in the treatment of chronic hepatitis B. Value Health 2010;13:922–33.]	

LT	Death	21.00%	Bermingham et al. (65) [sourced from Veenstra DL, Sullivan SD, Dusheiko GM, et al. Cost-effectiveness of peginterferon alpha-2a compared with lamivudine treatment in patients with HBe-antigen-positive chronic hepatitis B in the United Kingdom. Eur J Gastroenterol Hepatol 2007;19:631–8]
PLT	Death	5.70%	Bermingham et al. (65) [sourced from Veenstra DL, Sullivan SD, Dusheiko GM, et al. Cost-effectiveness of peginterferon alpha-2a compared with lamivudine treatment in patients with HBe-antigen-positive chronic hepatitis B in the United Kingdom. Eur J Gastroenterol Hepatol 2007;19:631–8]

Abbreviations: CC = compensated cirrhosis; DCC = decompensated cirrhosis; HBV = hepatitis B virus; HDV = hepatits delta virus; HCC = hepatocellular carcinoma; LT = liver transplant; OR = odds ratio; PLT = post-liver transplant; TP = transition period

8.1.2.2 Validation of transition probabilities (step 2)

To validate projections from the economic model vs. those observed in HDV natural history studies, HDV natural history studies were evaluated for those considered most appropriate for comparison with the model. The factors included, but were not limited to, (1) availability of Kaplan-Meier survival data on the specific advanced liver disease endpoint, (2) availability of information on granular fibrosis stages and/or data specific to compensated cirrhosis patients, (3) data specific to untreated patients / patients without treatment response [as these would be assumed to be most representative of non-responders in the model].

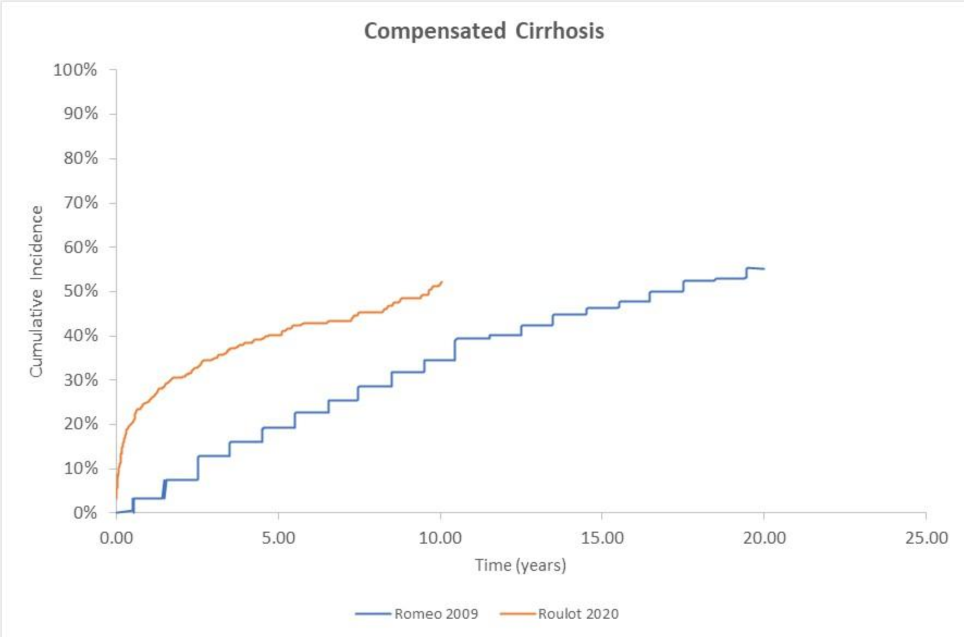
Kaplan-Meier curves from the selected natural history studies were digitised using Plot Digitizer. Baseline demographics (e.g., baseline fibrosis distribution, patient age, sex distribution) in the model were aligned with the natural history studies based on available data. In several studies, fibrosis stage data were only available for compensated cirrhotic (F4) vs. non-cirrhotic (F0-F3) patients. In these cases, the relative distribution of patients across F0-F3 was based on Romeo, Del Ninno (21). Model outcomes for advanced liver-disease events were compared against the digitised Kaplan-Meier curves from these natural history studies based on visual inspection.

Compensated Cirrhosis

Given granular information on the distribution of patients from F0-F4 health states in Romeo, Del Ninno (21), this study was selected for validation of the economic model outcomes as compared to HDV natural history. In this study, the cumulative probability of cirrhosis at 20 years was 55% with an incidence rate of 4% per year in overall (F0-F3) non-cirrhotic patients (Figure 3). Given that the values were not reported granularly (i.e., F2→F3, F3→F4), individual transition probabilities could not be derived.

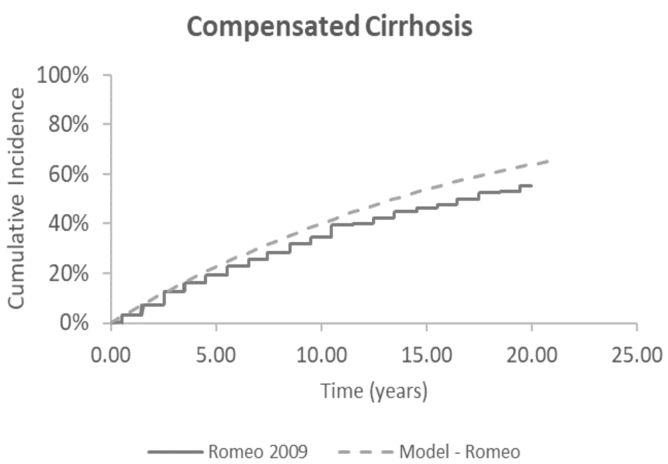
Notably, these estimates from Romeo, Del Ninno (21) may even be conservative, as the study by Roulot, Brichler (23) of a French retrospective cohort of HDV patients estimated a 5-year risk of cirrhosis of 49.4% in non-cirrhotic patients (notably including both treated and untreated patients, Figure 4). Further, in this study, where 407 (36.6%) of patients had significant or severe fibrosis (i.e., ≥F2) at baseline, among new cirrhotic patients after a median follow-up of 3.0 years, 166/174 (95.4%) had been classified as having ≥F2 at referral. These data support a fast rate of progression in patients with advanced fibrosis.

Figure 3 Cumulative incidence of compensate cirrhosis in Romeo *et al.* 2009 and Roulot *et al.* 2002 studies



As shown in Figure 4 below, the model projections for the incidence of compensated cirrhosis amongst the patients in F0-F3 at model start are generally in alignment with findings from Romeo, Del Ninno (21). The incidence is slightly higher overall which could be supported given the results observed in Roulot, Brichler (23).

Figure 4 Comparison of model outcomes for compensated cirrhosis with Romeo *et al.* 2009



Decompensated Cirrhosis

In Kamal, Westman (38), 337 anti-HDV positive patients were retrospectively studied with a mean follow-up time of 6.5 years (range 0.5-33.1). Among anti-HDV positive patients, 29.6% of patients had liver cirrhosis at baseline and 39.1% of anti-HDV positive patients with cirrhosis at baseline experienced hepatic decompensation, while only 3% of anti-HDV positive patients without cirrhosis at baseline experienced hepatic decompensation. Cumulative decompensation-free survival is shown in Figure 5. Projections from the model are similar to those from Kamal, Westman (38) (Figure 6). Further, the rate of hepatic decompensation in patients with cirrhosis at baseline was 10.2% per person-year, similar to the rate estimated for use in the economic model (10.67%).

Figure 5 Kaplan-Meier decompensation-free survival curves based on HDV RNA status from Kamal *et al.* 2020

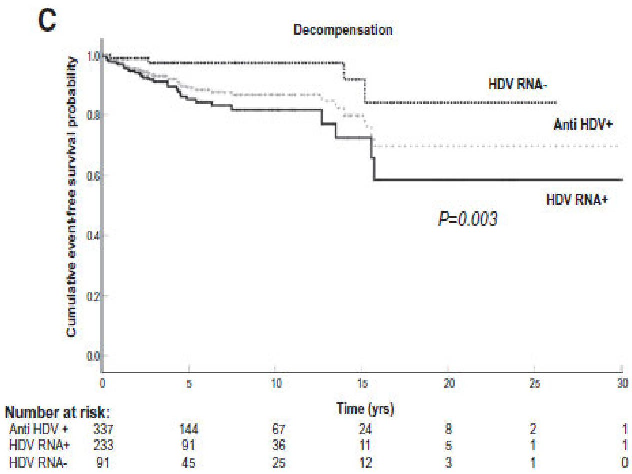
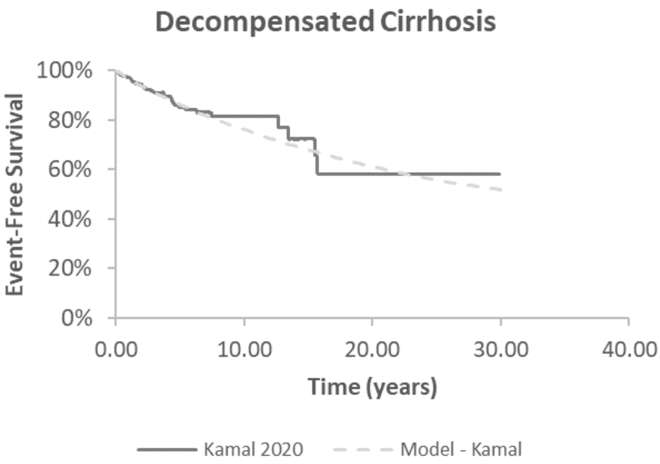


Figure 6 Comparison of survival of patients from Kamal *et al.* 2020 vs. predictions from economic model



Hepatocellular carcinoma

In Yurdaydin, Keskin (84), a hepatitis delta database was analysed for effects of treatment duration on virologic response and clinical outcomes. 99 chronic hepatitis delta patients who receive at least 6 months of interferon treatment were selected. Post-treatment median follow-up was 55 months (24-225 months). Of these patients, 35 achieved maintained virologic response (MVR). In the non-responder patients, 22%

(14/64) had cirrhosis present at baseline. Hepatocellular carcinoma-free survival outcomes for patients without MVR, assumed to be most appropriate for comparison with non-responders in the model, are shown in Figure 7. Given the lack of data regarding the distribution of patients from F0-F3, a similar distribution of non-cirrhotic patients was assumed based on Kamal, Westman (38). The model showed generally similar results for the cumulative incidence of hepatocellular carcinoma for non-responders compared to those without MVR from Yurdaydin, Keskin (84) (Figure 8).

Figure 7 Kaplan-Meier hepatocellular carcinoma-free survival curve from Yurdaydin *et al.* 2018 in patients with and without MVR

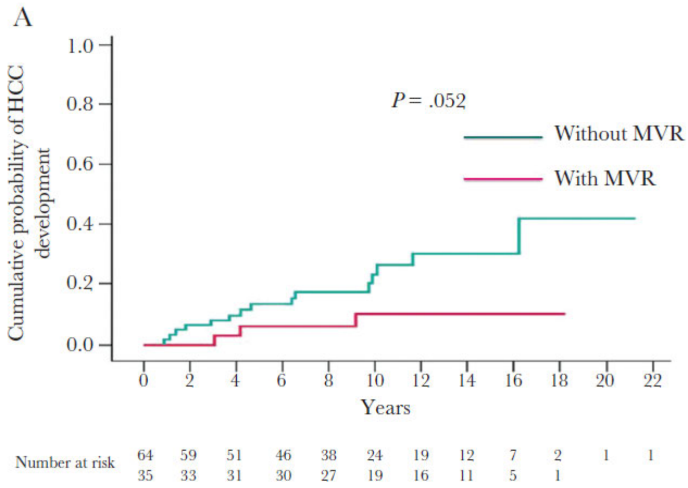
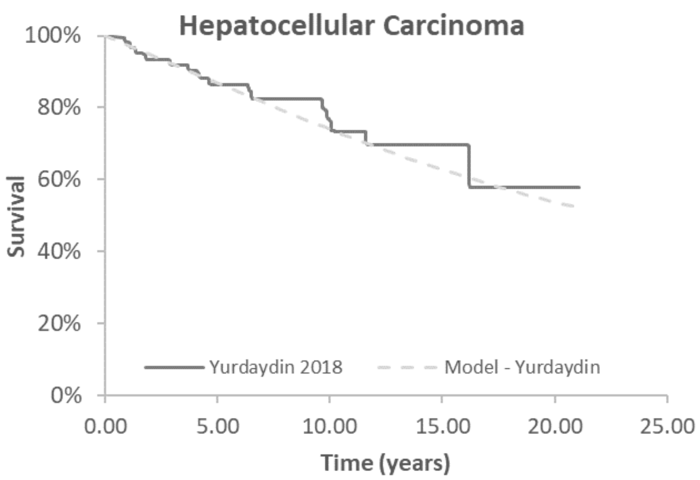


Figure 8 Comparison of survival of patients from Yurdaydin *et al.* 2018 vs. predictions from economic model



Liver-Related Mortality

Three natural history studies were evaluated to compare the projections from the economic model regarding mortality.

Survival of Compensated Cirrhosis (F4) Patients

The first study included 166 patients with compensated HDV-related cirrhosis diagnosed since 1994 and followed until death or 31 Dec 2004. Patients had a mean age of 40.7±7.9 years (85). The median survival was 58.3 months since the diagnosis of compensated cirrhosis, with a probability of survival after the diagnosis of compensated cirrhosis of 94.3%, 82.5%, and 51.5% at 1, 2, and 5 years, respectively (Figure 9). Projections from a purely compensated cirrhotic (i.e., 100% F4) population in the model demonstrated strong alignment with those projected from this study (Figure 10).

Figure 9 Kaplan-Meier survival curve of patients with compensated HBV-HDV cirrhosis from Gheorghe *et al.* 2005

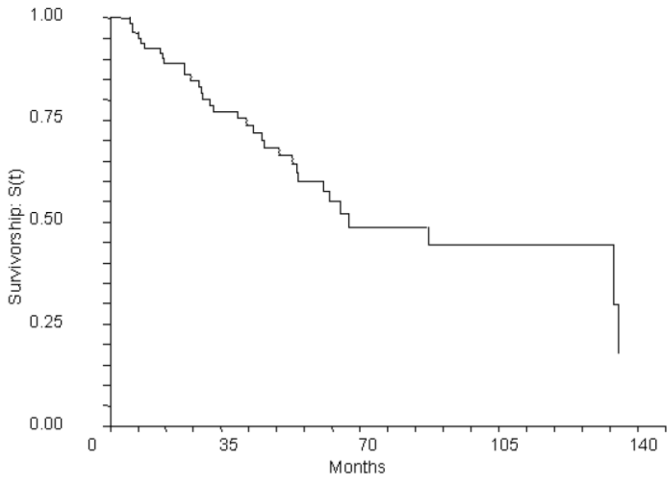
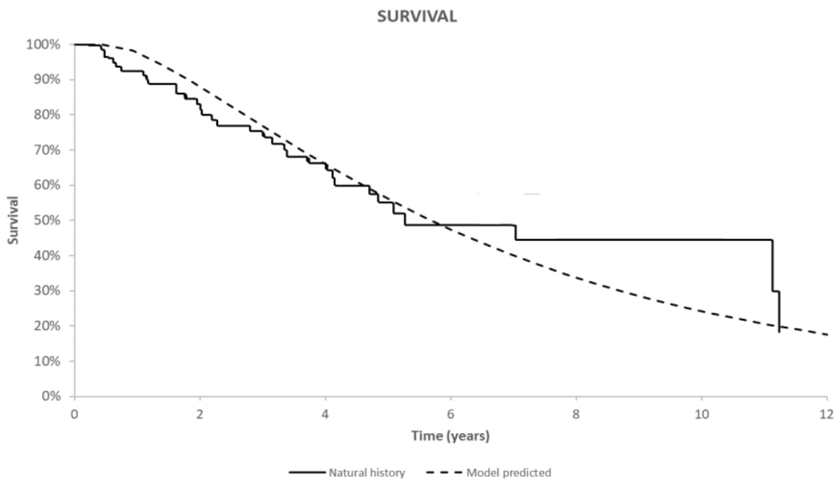


Figure 10 Comparison of survival of compensated cirrhosis patients from Gheorge *et al.* 2005 vs. predictions from economic model



Survival in broad F0-F4 population

To determine whether projections from the combined non-cirrhotic and cirrhotic populations aligned with natural history studies regarding mortality, two studies were selected based on availability of data for patients who were HDV RNA positive (23) and for those without MVR due to treatment (84). In Roulot, Brichler (23), 28.1% of patients had cirrhosis at referral, 36.6% had significant or severe fibrosis (≥F2), and 16.8% had no or minimal fibrosis (F0-F1). The 5-year risk of death in the entire population, including patients who may have received treatment, was 20.2%. Survival according to HDV RNA status at the end of follow-up showed that patients with positive HDV viral load had a higher risk of death (hazard ratio 3.30, p<0.001; Figure 11). Projections from the model are generally similar to those from (23) (Figure 12).

Figure 11 Survival without liver transplantation according to persistent HDV viremia before endpoint from Roulot *et al.* 2020

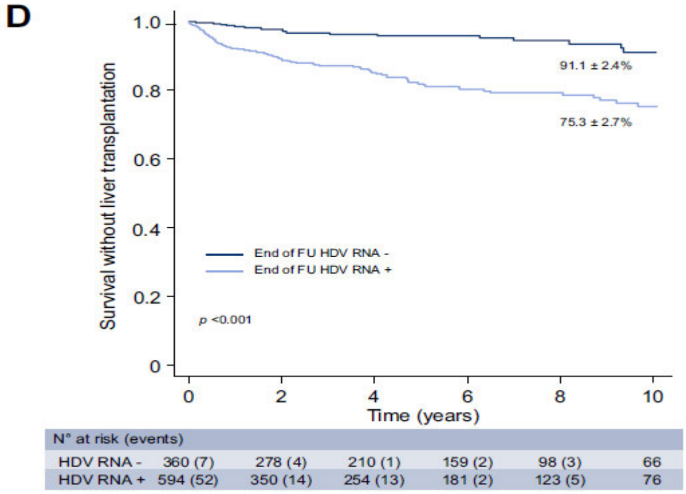
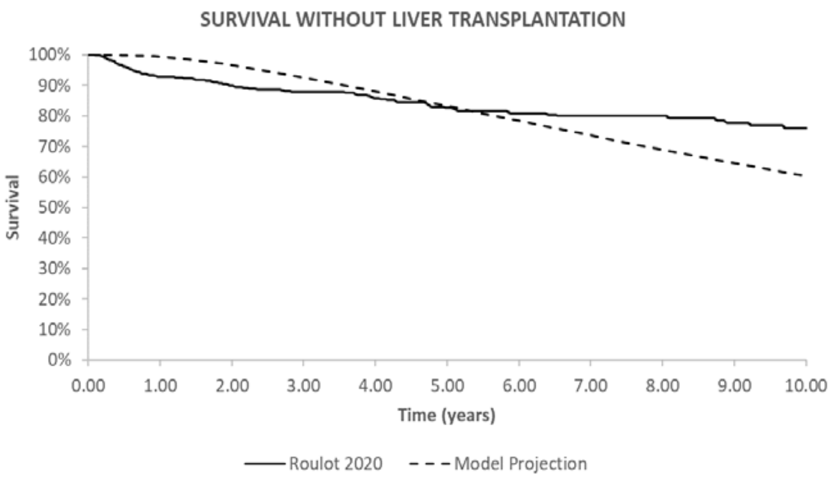


Figure 12 Comparison of survival of F0-F4 HDV RNA+ patients from Roulot 2020 vs. predictions from economic model



In Yurdaydin, Keskin (84), a hepatitis delta database was analysed for effects of treatment duration on virologic response and clinical outcomes. 99 chronic hepatitis delta patients who receive at least 6 months of interferon treatment were selected. Post-treatment median follow-up was 55 months (24-225 months). Of these patients, 35 achieved MVR. In the non-responder patients, 22% (14/64) had cirrhosis present at baseline. Survival outcomes for patients without MVR, assumed to be most appropriate for comparison with non-responders in the model, are shown in Figure 13. Given the lack of data regarding the distribution of patients from F0-F3, a similar distribution of non-cirrhotic patients was assumed based on Romeo, Del Ninno (21). Given the relatively low number of observations (Figure 13) after 10 years, these first ten years were analysed to compare model survival outcomes vs. the study. The model showed generally similar results for liver-related mortality for non-responders compared to those without MVR from Yurdaydin, Keskin (84) (Figure 14).

Figure 13 Liver-related mortality stratified by MVR status in Yurdaydin *et al.* 2018

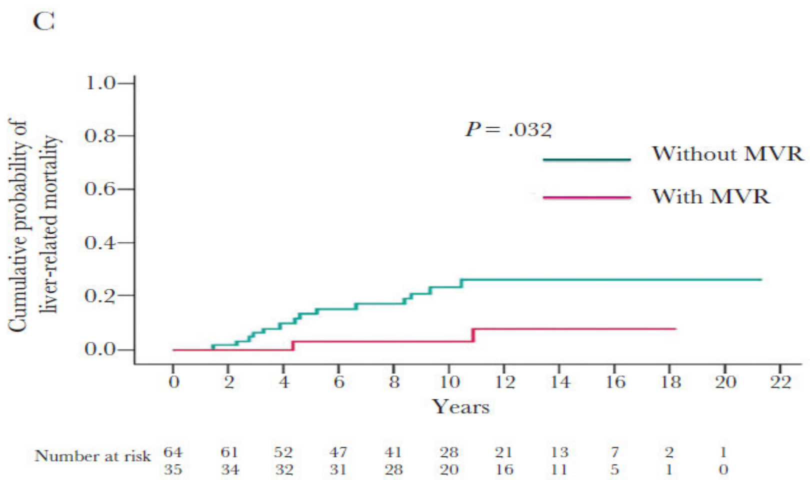
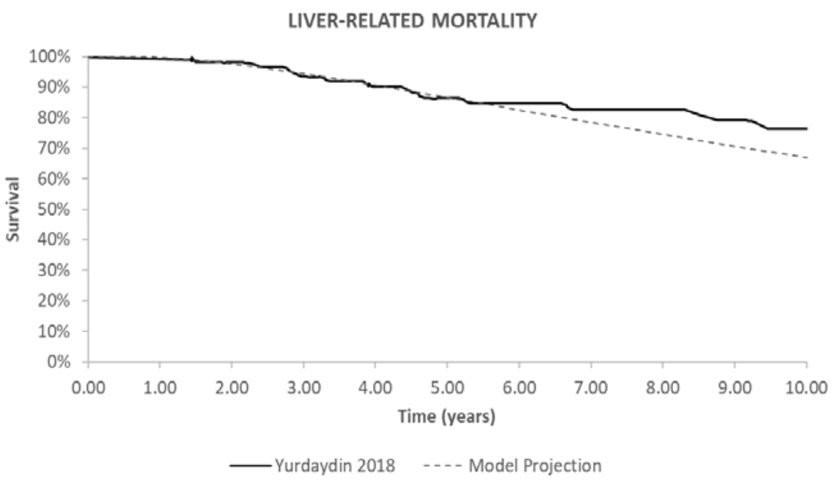


Figure 14 Comparison of survival of F0-F4 patients without MVR vs. predictions from economic model



8.1.2.3 Transition probabilities for responders (step 3)

8.1.2.3.1 Share of responders

The proportion of patients achieving the combined response endpoint (HDV RNA undetectable or 2log decline and ALT normalisation) was sourced from MYR301 (Appendix B.1.2). However, since patients on BSC only remained in that treatment arm until week 48 (Section 6.1.1.1), the subsequent values had to be calculated by extrapolation. According to a Nordic clinical expert, no improvement is to be expected after week 48 on BSC (39). Hence, the share observed in the BSC arm in MYR301 in week 48 was extrapolated for the remaining time points.

Table 17 shows the share of responders used in the model. These inputs can be found in the model in the CLINICAL sheet. The CLINICAL sheet also contains inputs for suboptimal responders. This serves as a placeholder as currently there is no data to model the clinical benefit of suboptimal responders but can be populated when such data is available. In the current model, suboptimal responders share the disease progression of non-responders (HR=1).

Table 17 Combined response endpoint data, MYR301 and extrapolation

Time	Bulevirtide		BSC only	
	Share with combined response	Reference	Share with combined response	Reference
Week 24	36.70%	MYR301	0.00%	MYR301
Week 48	44.90%	MYR301	2.00%	
Week 72	44.90%	MYR301	2.00%	Data on file (39)
Week 96	55.10%	MYR301	2.00%	
Week 120	57.10%	MYR301	2.00%	
Week 144	57.10 %	MYR301	2.00%	

Abbreviations: BSC = best supportive care

Reference: (86)

8.1.2.3.2 Disease progression for responders

The efficacy of bulevirtide was measured using a combined response endpoint that consists of virologic (HDV RNA undetectable or ≥2-log decline) and biochemical (ALT normalisation) markers, which is in line with guideline recommendations (FDA 2019). While the combined response endpoint, which was the primary endpoint of MYR301, is the key measure of efficacy, there is limited data linking the combined response endpoint to a reduction in HDV disease progression and clinical events, which is needed for the health economic model.

To inform the relationship between the combined response endpoint and disease progression, a modified Delphi panel approach was undertaken. The Delphi technique is a systematic way to determine whether consensus across individuals can be obtained regarding a value or topic. The same information and questions are asked to a number of clinical experts, who remain anonymous, in a series of rounds. The ultimate goal of a Delphi panel is to determine consensus. Three different conceptual approaches were discussed with an international panel (members from US, Europe and Turkey) of 11 clinicians experienced in treating HDV infection (Gilead Sciences Inc. 2024). The three approaches were: (1) assuming the combined response has an impact on uncontrolled HDV infection similar to the reduction in disease progression observed with patients achieving HDV-RNA undetectability; (2) assuming the combined response has an impact on uncontrolled disease progression similar to the rates of disease progression among those who have HBV mono-infection; and (3) assuming the combined response has an impact on rate reduction in HDV disease progression, which was similar to patients achieving ALT normalisation in HBV.

Of the 11 clinical experts, 9 (82%) selected Approach 1 (Relationship to RNA undetectability/negativity) as the preferred clinical analogue approach. Rationale for choosing Approach 1 included clinical rationale that achieving the composite would slow disease progression even among patients who did not achieve RNA undetectability, and that these data exist for the HDV population. The generally accepted definition of consensus in a Delphi panel is achieving agreement greater than 75%, and since 82% agreement was reached, consensus was achieved for this topic. To provide more robust estimates of the impact of HDV RNA undetectability on natural history data in HDV patients, a SLR and meta-analysis was performed. A SLR was first undertaken to identify cohort studies that reported relationships of HDV RNA negativity vs. positivity in terms of its impact on liver disease progression in chronic HDV patients. These data were then synthesized in a meta-analysis, where hazard ratios on specific liver disease progression events (i.e., any liver disease event, progression from CC to DCC, CC to HCC, etc.) were determined (87). More recently, at EASL 2024, Degasperi, De Silvestri (88) published the first and to our knowledge only study comparing the impact of treatment with bulevirtide on clinical outcomes. Degasperi, De Silvestri (88) compared outcomes for patients with compensated cirrhosis in the SAVE-D cohort (bulevirtide treated patients) with an historical cohort (Romeo et al. 2009). Furthermore, Degasperi, De Silvestri (88) performed an IPTW-adjusted analysis for the risk of decompensation in the treated vs. untreated cohort in the first 24 months and reported a hazard ratio of 0.32 for the treated population (88). At Week 96, 51% of treated patients achieved combined response, 12% ALT normalization only, and 26% virologic response only. 11% of patients were non-responders (by any criteria). At EASL 2025, Kamal et al. presented a retrospective study that combined data from D-SOLVE and the HDV1000 database. In this study clinical outcomes for 565 patients from Sweden, UK, Romania, France, and Germany were reported after a median follow-up time of 55 months. Kamal et al. reported a significantly higher risk of de-novo cirrhosis development among patients without cirrhosis at baseline (F0-F3) for patients with elevated ALT levels at baseline compared to those with normal ALT (HR=3.89; 95% CI: 1.74-8.73) and for patients with detectable HDV RNA at baseline compared to those with undetectable HDV RNA (HR=4.41; 95% CI: 1.57-12.40). In patients with cirrhosis at baseline, no patients with undetectable HDV RNA developed HCC or decompensated cirrhosis compared to 10.1% (95% CI: 5-16%) and 14.2% (95% CI: 7-21%) respectively for patients with detectable HDV RNA at baseline. The risk of de-novo overall liver-related events was significantly higher among patients with detectable HDV RNA at baseline compared to those with undetectable HDV RNA at baseline (HR=4.36; 95% CI: 1.57-12.16).

In the base case, the estimates for fibrosis progression and decompensation are based on the data from Degasperi, De Silvestri (88) and Kamal, Radu (58), whereas the risk of developing HCC and death are sourced from Gish, Wong (87). The estimates calculated from the data published by Degasperi, De Silvestri (88) and Kamal, Radu (58) are described in the following paragraphs. The basis for the calculation is the reported HR of 0.32 for bulevirtide treated vs. untreated patients of experiencing decompensation and clinical expert input that the relative risk of progressing from F4 (CC) to DCC is expected to be similar as the relative risk of fibrosis progression in F0-F3 patients among combined responders. The HR of 0.32 can be found in the table named 'BLV Treatment Effect on Liver-related Events IPTW-Adjusted Analysis' of Degasperi, De Silvestri (88). A complementary illustration of the process and results are displayed in Figure 15.

To estimate the HR for combined responders, the treated population group was separated into four mutually exclusive groups: non-responders (11%), virological responders (26%), ALT normalized (12%), and combined responders (51%). Both the HR for treated vs. untreated and the group proportions were sourced from Degasperi, De Silvestri (88). Patients in the non-responder group were assumed to not gain any benefit from treatment and were assigned a HR of 1 compared to the untreated population. The HR for any type of responders was derived under the assumption that the overall treatment effect represents a weighted average of subgroup-specific effects, resulting in the following equation for the responder HR: $HR_r = (HR_{treated} – p_{nr} \text{ x } HR_{nr}) / (1 − p_{nr})$, where p is equal to the proportion of non-responders (p=0.11), resulting in $HR_r = 0.24$.

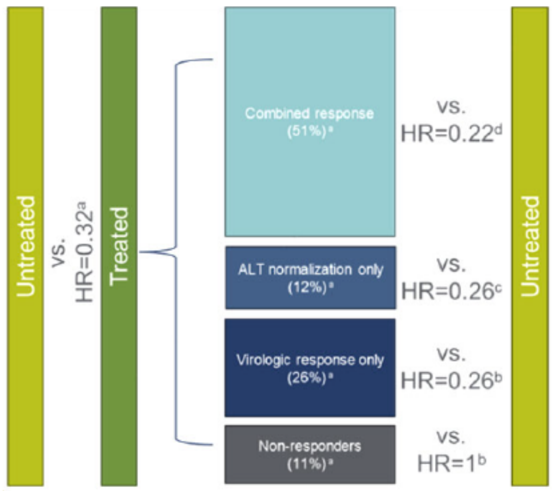
The next step is to derive HRs vs. untreated for the different groups that showed any type of response to treatment. For the ALT normalized group, the reciprocal of the HR for ALT elevation at baseline from Kamal, Radu (58) was used (HR=1/3.89=0.26). It was assumed that the benefit of achieving a virological response only was the same as that of achieving ALT normalization only, i.e. all partial responders were assumed to have a HR of 0.26. In the final step, the HR for the combined responders was calculated as $HR_{CR} = (HR_r – p_{pr} \text{ x } HR_{pr}) / (1 – p_{pr})$, where p in this equation is the proportion (43%) of partial responders (virologic or normalized ALT) among all responders, resulting in a HR for combined responders of 0.22 vs. the untreated population. This HR of 0.22 is similar to the HRs reported by Kamal et al. for the risk of de-novo cirrhosis development (1/4.42=0.226) and de-novo overall liver related events (1/4.36=0.229) among patients with undetectable HDV RNA compared with those with detectable HDV RNA.

The on-treatment hazard ratios for patients achieving the combined response endpoint are shown in Table 18. Gish et al. (87) performed a systematic literature review and meta-analysis to examine the relation between HDV RNA status and risk of advanced liver disease events in patients who are HBsAg and HDV antibody positive. Compared to patients with HDV RNA-, HDV RNA+ was estimated to be associated with a significantly higher risk of progression to compensated cirrhosis [risk ratio: 1.74 (CI: 1.24, 2.45)] decompensated cirrhosis [HR: 3.82 (1.60, 9.10)], HCC [HR: 2.97 (1.87, 4.70)], liver transplantation [HR: 7.07 (1.61, 30.99)], and liver-related mortality [HR: 3.78 (2.18, 6.56)]. In the model, the hazard ratios for responders compared to non-responders are used. Hence, the inverse of the estimates from Gish et al. (87) are employed, i.e.

$\frac{1}{2.97} = 0.34$ for HCC and $\frac{1}{3.78} = 0.26$ for mortality.

The input can be found in the model in the CLINICAL sheet.

Figure 15 Illustration of calculation of HRs for fibrosis progression and decompensation for combined responders vs. untreated patients



Reference: a:(88); b: assumption; c:(58); d:calculated

Table 18 Responders disease progression treatment hazard ratios

Health State		Hazard Ratio	Source
From	To		
Fx	Fx+1	0.22	Calculation based on Degasperi et al. (88)
F0-F2	HCC	0.34	Gish et al. (87)
F3	HCC	0.34	Gish et al. (87)
CC (F4)	DCC	0.22	Calculation based on Degasperi et al. (88)

HCC	0.34	Gish et al. (87)
Death	0.26	Gish et al. (87)

Abbreviations: F0: fibrosis stage 0; F1: fibrosis stage 1; F2: fibrosis stage 2; F3: fibrosis stage 3; NC: non-cirrhotic; CC: compensated cirrhosis; CI, confidence interval; DCC: decompensated cirrhosis; HCC: hepatocellular carcinoma.

8.1.2.3.3 Transition probabilities for responders

The TPs for the responder population are calculated by combining the natural history of HDV and the HR calculated in the previous step. When applying the HR of reduced disease progression (Table 18) to the natural history of HDV (Table 16), the transition probabilities can thereafter be calculated using the equation: 1-EXP(LN(1-Annual TP(NAT_HIS))*HR(responders), for which the results are presented in Table 19 and in the CALCULATIONS sheet in the model. Due to data limitations, transitions between non-cirrhotic fibrosis stages (F0-F3) were assumed to be the same, which is shown in Table 19 as the transitions between Fx to Fx+1. In contrast, more granular data availability would have enabled different TPs for e.g. transitions F0 to F1 and F2 to F3.

Table 19 Annual transition probabilities for responders

Health State		Input	Source
From	To		
Fx	Fx+1	3.53%	Calculated using the following relationship: 1-EXP(LN(1-Annual TP(NAT_HIS))*HR(responders) Annual TP(NAT_HIS) from Table 16 HR(responders) from Table 18
	HCC	0.47%	
CC (F4)	DCC	2.45%	
	HCC	2.15%	
	Death	1.98%	

Abbreviations: F0: fibrosis stage 0; F1: fibrosis stage 1; F2: fibrosis stage 2; F3: fibrosis stage 3; NC: non-cirrhotic; CC: compensated cirrhosis; DCC: decompensated cirrhosis; HCC: hepatocellular carcinoma

Patients who progress to advanced liver disease are assumed to discontinue treatment, as per treatment stopping rules detailed in Section 8.4. Therefore, no reduction in disease progression is assumed for patients in these stages (DCC, HCC, LT or PLT).

Fibrosis regression

In addition to the reduction in disease progression due to treatment, there is the possibility that responding to treatment may induce a regression in liver fibrosis and cirrhosis for those achieving the combined response endpoint. In the MYR301 trial, 50% of patients treated with bulevirtide 2 mg showed fibrosis regression after 48 weeks according to the METAVIR scale (35). Fibrosis regression was also described by Farci, Roskams (18), where four out of six treated HDV patients with a sustained biochemical response regressed from F4 to F0 in 11.5 years. Regression is also supported by Marcellin et al. who reported regression of cirrhosis for HBV mono-infected patients who experienced viral suppression while on treatment. In their study, 51% of patients were found to have fibrosis regression after five years. Among cirrhotic patients who experienced fibrosis regression, 87% had normalized ALT (66). Expert opinion aligned with the findings that patients who respond to therapy and achieve combined response endpoint could experience an improvement in cirrhosis/fibrosis due to treatment, and regress (39).

Regression in liver fibrosis is internalised to the model for responders using transition probabilities based on the data reported by Farci, Roskams (18) and Marcellin, Gane (66). In Farci, Roskams (18) the observed regression over 11.5 years corresponds to an average time of 2.9 years per step regression and an annual transition probability of 31.76% from F4 to F0. In Marcellin, Gane (66) fibrosis was staged with the Ishak system and for the calculation of transition probabilities mapping between METAVIR F stages and Ishak was performed as in Sebastiani (89) and is shown in Table 20.

Table 20 Mapping of liver fibrosis stages between Ishak and METAVIR

Description	Ishak	METAVIR
No fibrosis	0	F0
Portal fibrosis without septa	1-2	F1
Portal fibrosis with few septa	3	F2
Septal fibrosis without cirrhosis	4	F3
Cirrhosis	5-6	F4

Among cirrhotic patients, 71 of 96 experienced fibrosis regression with an average of 3.0 steps reduction per patient over the five-year follow-up period or an average time of 1.7 years per regression step in Ishak fibrosis score. This corresponds to 2.5 years per step when mapped to the METAVIR system and an annual transition probability of 41.47%. Among patients without cirrhosis at baseline, 212 of 252 (85%) were in Ishak stages 1-3, corresponding to F1-F2 in the METAVIR system. 105 of 252 patients experienced fibrosis regression, with an average of 1.8 steps reduction per patient or an average time of 3.9 years per regression step in Ishak score. This corresponds to 5.9 years per per step when mapped to the METAVIR system and an annual transition probability of 8.67%. While the total number of possible steps of regression in the non-cirrhotic patients in non-cirrhotic patients is lower and therefore potentially capped, the overall data suggest that regression is slower in patients with less fibrosis. In the model, transition probabilities for regression are based on Farci, Roskams (18) for patients in F3-F4 (31.76%) and the non-cirrhotic patients in Marcellin, Gane (66) for patients in F1-F2 (8.76%).

8.1.2.3.4 Scenario analyses

Given the uncertainty surrounding the relationship between reduction in disease progression following achieving a combined response versus non-response, an additional scenario was considered for the treatment hazard ratio for responders. This scenario disregards the new data based on Degasperi, De Silvestri (88) and Kamal, Radu (58), and only relies on the HRs from the meta-analysis performed by Gish, Wong (87). These values are summarized in Table 21.

Table 21 Disease Progression Treatment Hazard Ratios, Gish et al. only scenario analysis

Health State		Hazard Ratio (HDV Responder vs. Non-Responder)	Reference
From	To		
Fx	Fx+1	0.38	Gish et al. (87)
F0-F2	HCC	0.34	Gish et al. (87)
F3	HCC	0.34	Gish et al. (87)
CC (F4)	DCC	0.26	Gish et al. (87)
	HCC	0.34	Gish et al. (87)
	Death	0.26	Gish et al. (87)

Abbreviations: F0: fibrosis stage 0; F1: fibrosis stage 1; F2: fibrosis stage 2; F3: fibrosis stage 3; F4: fibrosis stage 4; NC: non-cirrhotic; CC: compensated cirrhosis; DCC: decompensated cirrhosis; HCC: hepatocellular carcinoma

In Figure 16 and Figure 17, the proportion of patients per health state over time are presented, for patients on bulevirtide and BSC only respectively.

Figure 16 Proportion of patients per health state - bulevirtide

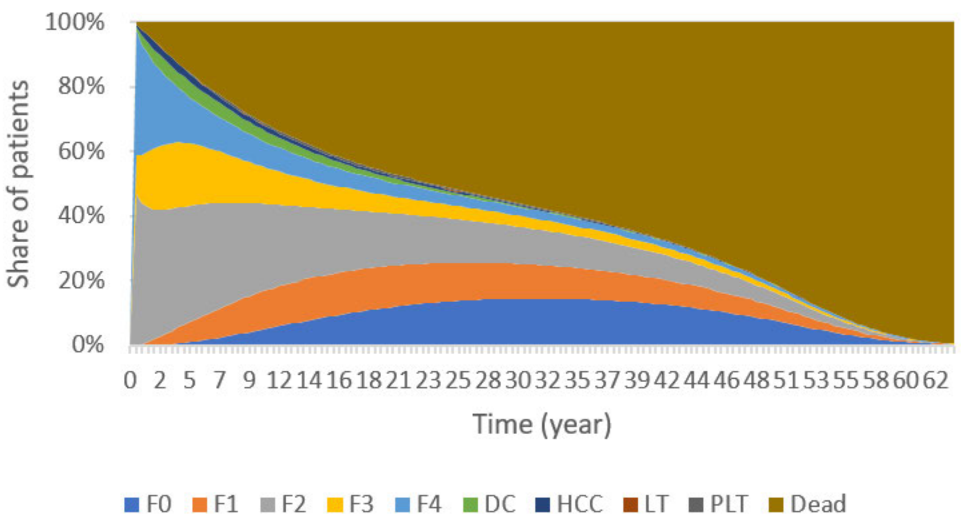
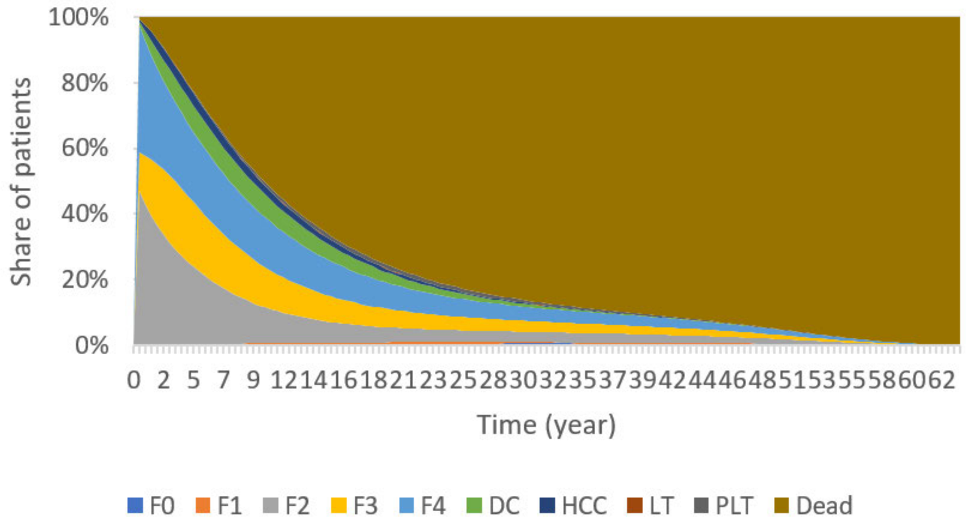


Figure 17 Proportion of patients per health state - BSC only



8.2 Presentation of efficacy data from [additional documentation]

Not applicable.

8.3 Modelling effects of subsequent treatments

Not applicable.

8.4 Other assumptions regarding efficacy in the model

As stated in the EPAR, treatment should be continued as long as associated with clinical benefit (15). Lack of clinical benefit is defined as not having achieved the combined response endpoint at week 96 and sustained HDV RNA undetectability over 96 weeks. 96 weeks of sustained undetectability after end of treatment was chosen as data shows that 90% of those patients are observed to remain with undetectable HDV RNA levels after treatment discontinuation (90). This assumption was also supported by the Swedish clinical expert who stated that discontinuation for patients with sustained undetectability, with patient monitoring after discontinuation, is reasonable (39). The Swedish clinical expert further expressed a strong support for the undetectable stopping rule for patients in F2-F3 (39) while there is more uncertainty around stopping patients in F4, as the impact of a relapse would be more significant why a longer treatment period (3-5 years) with sustained HDV RNA undetectability might be more reasonable. It is assumed that the clinical benefit of treatment will be continuously evaluated during treatment. These rules were implemented in the model at discrete time points in the following manner:

1. At 96 weeks, patients who have not achieved a combined response discontinue treatment. Combined response is defined as HDV RNA undetectable or decrease by ≥2 log10 IU/mL from baseline and ALT normalisation.
2. At week 144, 192 and 240, patients who have achieved 96 weeks of HDV RNA undetectability discontinue treatment.

The percentage of virological and combined endpoint responders were sourced from the MYR301 trial. As the study period did not allow for directly observing the proportion of patients who have achieved 96 weeks of HDV RNA undetectability at weeks 144, 196, and 240 this had to be estimated, which was done in three steps. The assumptions are summarized in the bullet points below and a detailed description of each step is given thereafter.

- In the first step, the proportion of patients that reached undetectability within the study period that remained undetectable for 96 weeks or longer was calculated to estimate the rate of sustained undetectability among patients achieving undetectability. In the bulevirtide 2mg arm this was observed to be 71%.
- In the second step, for each relevant time point (weeks 144, 192, and 240) the proportion of patients among the combined responders that was expected to achieve sustained undetectability was calculated. This was done by taking the observed number of patients that achieved undetectable HDV RNA levels at weeks 48, 96, 144, as these weeks correspond to 96 weeks before the defined time points of treatment discontinuation, and multiplying with the rate of sustained undetectability from the first step.
- The third step determined the percentage of patients that after treatment discontinuation would relapse to detectable HDV RNA levels and hence would need to return to active treatment. In the MYR301 trial, 90% of patients that were undetectable for 96 weeks or longer remained at undetectable levels at the end of the 96 weeks off-treatment follow-up period.

The first step involves calculating the percentage of patients that remain undetectable for 96 weeks or longer after reaching undetectable levels of HDV RNA. Data available from the MYR301 trial included a total of 144 weeks of treatment for the bulevirtide 2mg arm (35). This allowed for patients that achieved undetectable levels of HDV RNA at week 24 and week 48 to be observed for at least 96 weeks and thus allowed for establishing the proportion that remained at undetectable levels for at least 96 weeks of on-treatment follow-up. Three patients achieved undetectable levels at week 24 of which two remained at those levels for at least 96 weeks. The corresponding numbers for those achieving undetectable levels at week 48 were four patients of which three remained at undetectable levels for 96 weeks. In summary, five patients out of seven (71%) remained at undetectable level for at least 96 weeks. This percentage estimate was used to extrapolate the number of patients that will remain undetectable after achieving undetectable levels of HDV RNA.

The second step of the calculations are shown in Table 22, which shows each sub-step of the second step per row. In this step the percentage from the previous step is applied to the number of patients observed to reach undetectable levels at a given timepoint, extrapolated 96 weeks forward in time representing the potential timepoint of treatment discontinuation. This aims to calculate the percentage of responders that are discontinued by dividing the number of patients extrapolated to have achieved sustained HDV RNA undetectability by the number of patients that achieved the combined response endpoint in the MYR301 trial. The result from this step is 17.86% at week 144, 12.76% at week 192, and 15.31% at week 240.

Table 22 Calculation of percentage of responders taken off treatment

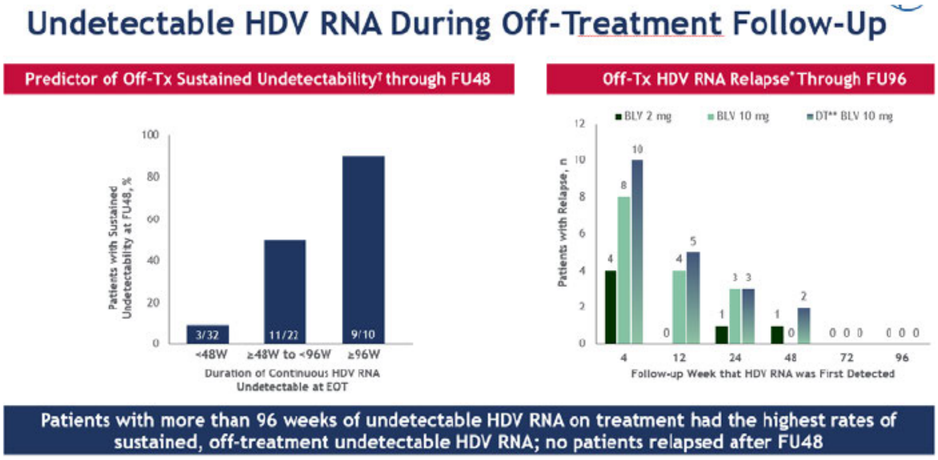
	Week 24	Week 48	Week 96	Week 144	Week 192	Week 240	Description
Achieving undetectable levels of HDV RNA	3	4	5	6	N/A	N/A	# of patients that at a given time point achieved undetectable levels of HDV RNA.
≥96 weeks undetectable	N/A	N(A	N/A	5 (observed	4 (5*71%)	4 (6*71%)	Calculated number of patients that remain undetectable 96 weeks after achieving undetectable HDV RNA levels. Rounded numbers.
Observed combined responders	17	22	27	28	28†	28†	Observed number of patients that achieved the combined response endpoint in the MYR301 trial during treatment. Values after treatment end (week 144) are carried forward
Projected proportion of responders with sustained HDV RNA undetectability	N/A	N/A	N/A	17.86 % (5.00/28)	12.76% (3.57/28)	15.31% (4.29/28)	Calculation of the % of patients to be taken off treatment at a given timepoint.

†= Observation carried forward from last datapoint of treatment

Abbreviations: HDV = hepatitis delta virus; N/A = not applicable; RNA = ribonucleic acid

The last step quantifies the percentage of patients that after the observation period of 96 weeks relapses and thus restarts treatment. This estimate was informed by data from the MYR301 trial as presented by Wedemeyer, Aleman (90), shown in Figure 18.

Figure 18 Patients with sustained undetectability through follow-up week 48



*HDV RNA relapse was defined as HDV RNA undectable and end of treatment (EOT) and ≥1 HDV RNA sample during the follow-up period with observed detectable HDV RNA
** Delayed treatment arm did not receive any bulevirtide (BLV) through week 48.
Sources: (90)

Figure 18 shows that if the patients stay at undetectable levels for 96 weeks or more, nine out of ten patients then remained undetectable through the entire follow-up period. This number informed the relapse rate of 10% used in the model.

The estimates from this calculation were applied as described above at timepoints Week 144, Week 192, and Week 240. The timepoints represent the time at which the patients have been observed to sustain undetectable HDV RNA levels for at least 96 weeks. In the cycle following the 144-week cycle 17.86% of the responder patients are taken off treatment, 12.76% in the cycle following the 192-week cycle, and 15.31% in the week 240-cycle. In each respective following cycle, the relapse rate of 10% is applied for the patients taken of treatment which then are returned to active treatment. Real world data for Austrian HDV patients who have stopped BLV treatment after reaching undetectable HDV RNA show that those who relapse while off therapy regain treatment response within 24 weeks when BLV treatment has been reinitiated.(91, 92). While patient numbers are small, this data indicate that treatment efficacy is not impaired by an off treatment period in patients who had previously responded to therapy. Therefore, we assume in the model that these patients will remain combined responders when on treatment again. In the model, this treatment discontinuation was simplified to only affect treatment costs and a disutility of the same magnitude as the responder benefit (see section 10.2.2) was applied to the proportion of patients who experienced a relapse in the cycle following treatment discontinuation.

An overview of the treatment stopping rules are shown in Table 23. The model includes alternative settings for 48, 72, 96, or 120 weeks. Disease progression to advanced disease, DCC, HCC, LT, and PLT health states, also result in the end of treatment.

Table 23 Bulevirtide treatment stopping rules

Timepoint	Stopping rule	Responders (%)	Source/note

Week 96	Combined responders	55.10% (35)	MYR301 (35)
Week 144	96 weeks undetectable HDV RNA	17.86% (35)	MYR301 (35) Note: of which 10% are restarting treatment
Week 192	96 weeks undetectable HDV RNA	12.76% (35)	Calculated based on MYR301 (35) Note: of which 10% are restarting treatment
Week 240	96 weeks undetectable HDV RNA	15.31% (35)	Calculated based on MYR301 (35) Note: of which 10% are restarting treatment

Abbreviations: HDV = hepatitis delta virus; RNA = ribonucleic acid

The model also takes into consideration an annual rate of HbsAg seroclearance. The rate of HbsAg seroclearance is set to 1.13% in the base case based on findings from a recent meta-analysis on spontaneous clearance (93). Patients who achieve HbsAg seroclearance are assumed to come off HDV treatment.

For patients on bulevirtide, following treatment discontinuation due to being defined as non-responders, patients are considered off-treatment and follow natural history disease progression.

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

Table 24 is not applicable.

Table 24 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]	[X months/years]	[X months/years]	[X months/years]
[Name of comparator]	[X months/years]	[X months/years]	[X months/years]

The average time in the respective health states in the two arms is presented in Table 25. In addition, the mean time on bulevirtide treatment is presented.

Table 25 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction

Treatment	Treatment length [months]	F0 [months]	F1 [months]	F2 [months]	F3 [months]	F4 [months]	DCC [months]	HCC [months]	LT [months]	PLT [months]
Bulevirtide	122.6	62.1	58.7	105.2	40.6	36.2	8.8	4.7	0.1	2.6
BSC only	N/A	2.2	2.1	47.2	47.3	53.8	16.2	6.6	0.2	4.5

Abbreviations: N/A = Not applicable

9. Safety

9.1 Safety data from the clinical documentation

The documentation of the safety of bulevirtide is based on the MYR301 trial. Table 27 provides an overview of safety events. AEs used in the health economic model are summarized in Table 29.

The Safety Analysis Set (SAS) included all participants randomized to the BSC arm or randomized to bulevirtide who received at least 1 dose of bulevirtide after randomization. The analysis on the safety population was based on the actual treatment received (i.e., participants were analysed "as treated"). This was the primary analysis set for safety with the exception of safety analyses conducted only during the post treatment period. The Posttreatment Safety Analysis Set included participants in the SAS who had at least 1 non-missing safety assessment performed after the last dose of bulevirtide. This was the primary analysis set for safety displays during only the posttreatment period; and for analysis of posttreatment liver-related clinical events (35).

During the first 48 weeks, the percentages of participants in each group who experienced at least 1 adverse event (AE) were as follows: BSC arm: 41 of 51 participants (80.4%) and bulevirtide 2 mg arm: 41 of 49 participants (83.7%). Overall, the majority of the AEs were Grade 1 (mild) or 2 (moderate) in severity. In the bulevirtide 2 mg arm, 24 of 49 participants (49.0%) had AEs assessed as related to bulevirtide by the investigator. A similar percentage of participants in each group experienced serious adverse events (SAEs) (BSC arm: 1 of 51 participants [2.0%] and bulevirtide 2 mg group: 2 of 49 participants [4.1%]). None of the SAEs were considered related to bulevirtide by the investigators (35).

Through Week 144, the majority of the AEs were Grade 1 or 2 in severity. The proportions of participants with AEs considered related to bulevirtide in the bulevirtide 2 mg arm were 27 of 49 participants (55.1%). SAEs were experienced by 3 of 49 participants (6%) in the bulevirtide 2 mg arm. None of the reported SAEs were considered related to bulevirtide (35). Treatment emergent adverse events (TEAEs) with events in ≥ 10% of participants are depicted in Table 26.

Table 26 MYR301 - Treatment-emergent adverse events in ≥ 10% of participants in any group while on treatment by preferred term (Safety Analysis Set)

Preferred term	Bulevirtide 2 mg (N=49)		BSC[a] (N=51)
	Baseline to Week 48	Baseline to Week 144	Baseline to Week 48
Number of participants with any treatment-emergent AEs	41 (83.7%)	41 (83.7%)	41 (80.4%)

Preferred term	Bulevirtide 2 mg (N=49)		BSC[a] (N=51)
	Baseline to Week 48	Baseline to Week 144	Baseline to Week 48
Vitamin D deficiency	7 (14.3%)	7 (14.3%)	13 (25.5%)
Headache	9 (18.4%)	9 (18.4%)	0
Leukopenia	7 (14.3%)	7 (14.3%)	10 (19.6%)
Thrombocytopenia	5 (10.2%)	5 (10.2%)	8 (15.7%)
Lymphopenia	4 (8.2%)	4 (8.2%)	4 (7.8%)
Neutropenia	2 (4.1%)	2 (4.1%)	3 (5.9%)
Fatigue	5 (10.2%)	5 (10.2%)	1 (2.0%)
Arthralgia	3 (6.1%)	3 (6.1%)	0
Pruritus	6 (12.2%)	6 (12.2%)	0
Alanine aminotransferase increased	2 (4.1%)	2 (4.1%)	4 (7.8%)
Anaemia	3 (6.1%)	3 (6.1%)	3 (5.9%)
COVID-19	1 (2.0%)	1 (2.0%)	2 (3.9%)
Eosinophilia	5 (10.2%)	5 (10.2%)	0
Nasopharyngitis	4 (8.2%)	4 (8.2%)	2 (3.9%)
Injection site erythema	2 (4.1%)	2 (4.1%)	0
Injection site reaction	3 (6.1%)	3 (6.1%)	0
Nausea	3 (6.1%)	3 (6.1%)	2 (3.9%)
Abdominal pain upper	0	0	1 (2.0%)
Urinary tract infection	1 (2.0%)	1 (2.0%)	1 (2.0%)

Note: Adverse events were coded according to MedDRA Version 27.1.

[a] From Week 48 through the end of treatment, participants received bulevirtide 10 mg.

Abbreviations: AE = adverse events; BSC = best supportive care

Source: (35)

A brief overall summary of AEs is presented in Table 27 for the on-treatment period.

Table 27 Overview of safety events while on treatment (On-Treatment Period)

	Bulevirtide 2 mg (N=49) (35)		BSC[a] (N=51) (35)	Difference at Week 48, % (95% CI)
	Baseline to Week 48	Baseline to Week 144	Baseline to Week 48	
Number of adverse events, n	159	290	105	N/A
Number and proportion of patients with ≥1 adverse events, n (%)	41 (83.7)	48 (98%)	41 (80.4)	3.3% (-11.72%, 18.32%)
Number of serious adverse events*, n	4	5	2	N/A
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	2 (4.1)	3 (6.1)	1 (2)	2.1% (-4.65%, 8.85%)
Number of CTCAE grade ≥ 3 events, n	5	13	6	N/A
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events[§], n (%)	5 (10.2)	12 (24.5)	4 (7.8)	2.4% (-8.82%, 13.62%)
Number of adverse reactions, n	58	82	0	N/A
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	24 (49)	27 (55.1)	0	49% (35%, 63%)
Number and proportion of patients who had a dose reduction, n (%)	0	0	0	0
Number and proportion of patients who discontinue treatment	1 (1)	4 (4)	0	1% (-1.79%, 3.79%)

regardless of reason, n (%)				
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	0	0	0	0

* 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 (see the ICH's complete definition).

§ CTCAE v. 5.0 must be used if available.

[a] From Week 48 through the end of treatment, participants received bulevirtide 10 mg.

Abbreviations: BSC = best supportive care, NR = not reported

Source: (35)

Table 28 presents the number of patients with SAEs and the absolute number of SAEs while on treatment during the first 48 weeks of the study, up to Week 144 for the bulevirtide 2 mg arm. No SAE exceeded the frequency threshold of ≥ 5%. None of the SAEs while on treatment were considered to be related to study drug by the investigators. The majority of SAEs while on treatment were reported in 1 participant across arms. Two participants in the investigated arms experienced more than 1 SAE: 1 participant in the BSC arm experienced cholelithiasis and COVID-19, and 1 participant in the bulevirtide 2 mg arm experienced depression, headache, and hemiparesis (35).

Table 28 Serious adverse events (On-treatment period)

Adverse events	Bulevirtide 2 mg (N=49) (35)				BSC[a] (N=51) (35)	
	Baseline to Week 48		Baseline to Week 144		Baseline to Week 48	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Adverse event, n (%)	2 (4.1)	4	3 (6.1)	5	1 (2)	2

[a] From Week 48 through the end of treatment, participants received bulevirtide 10 mg.

Abbreviations: AE = adverse event; BSC = best supportive care; COVID-19 = coronavirus disease 2019

Source: (35)

Neutropenia, thrombocytopenia and leukopenia were considered relevant for this application (Table 29). No further safety data was considered relevant.

Table 29 Adverse events used in the health economic model

	Frequency used in economic model for intervention	Frequency used in economic model for comparator	Source	Justification
Neutropenia	0%	3.92%	Data on file (35)	Disorders with CTCAE grade 3 or higher
Thrombocytopenia	2.04%	5.88%		
Leukopenia	0%	1.96%		

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

Not applicable in this application.

Table 30 Adverse events that appear in more than X % of patients

Adverse events	Intervention (N=x)			Comparator (N=x)			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	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Abbreviations: N/A = not applicable

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

The EuroQol 5-dimension, 3-level QoL (EQ-5D-3L), the EuroQol Visual Analogue Scale (EQ-VAS), the Fatigue Severity Scale (FSS), and the Hepatitis Quality of Life Questionnaire (HQLQ) were used to evaluate the effects of bulevirtide (vs delayed treatment/BSC) on the HRQoL of patients participating in MYR301 (74).

Table 31 Overview of included HRQoL instruments

Measuring instrument	Source	Utilisation
EQ-5D-3L	MYR301	To evaluate the effects of bulevirtide (vs delayed treatment/BSC) on the HRQoL of patients participating in MYR301
EQ-VAS	MYR301	To evaluate the effects of bulevirtide (vs delayed treatment/BSC) on the HRQoL of patients participating in MYR301
FSS	MYR301	To evaluate the effects of bulevirtide (vs delayed treatment/BSC) on the HRQoL of patients participating in MYR301
HQLQ	MYR301	To evaluate the effects of bulevirtide (vs delayed treatment/BSC) on the HRQoL of patients participating in MYR301

Abbreviations: BSC = best supportive case; EQ-5D-3L = EuroQol 5-dimension, 3-level; EQ-VAS = EuroQol Visual Analogue Scale; FSS = The Fatigue Severity Scale; HQLQ = The Hepatitis Quality of Life Questionnaire;HRQoL = health-related quality of life

In the following sections the clinical EQ-5D-3L results, which were mapped to EQ-5D-5L and valued with the Danish EQ-5D-5L value set to obtain the EQ-5D-5L index scores required to inform the health economic model (94-96), are presented together with the HRQoL instruments used in the study but not included in the health economic model.

10.1 Presentation of the health-related quality of life

10.1.1 Study design and measuring instrument

10.1.1.1 EQ-5D-3L

EQ-5D-3L consists of a descriptive system of five questionnaire items (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) (97). Responses to these five dimensions are combined to represent a patient's health state, which is then converted into a single index value based on country-specific value sets. The collected EQ-5D-3L responses are mapped to EQ-5D-5L and valued with the Danish EQ-5D-5L value set to obtain the EQ-5D-5L index scores required by DMC guidelines (94, 95). Index scores range between 1 (perfect health) and 0 (death [negative values are possible for health states considered worse than dead]) (98). The study design of MYR301 did not deviate from the intended use of EQ-5D-3L.

10.1.1.2 EQ-VAS

The EQ-VAS is numbered from 0 (worst imaginable health) to 100 (best imaginable health) for which participants provide a global assessment of their health (EuroQol 1990). Anchor-based estimates of the minimum important difference in EQ-VAS range from 6.5 to 12 points (99, 100).

10.1.1.3 FSS

The FSS is a nine-item instrument designed to assess fatigue as a symptom of different chronic conditions and disorders. The scale includes fatigue's effects on daily functioning, its relation to motivation, physical activity, work, family, and social life. Respondents are asked to rate the ease with which they are fatigued and the degree to which the symptom poses a problem for them.

10.1.1.4 HQLQ

The HQLQ is a disease-specific HRQoL instrument developed to assess the physical, mental, and social well-being of individuals with chronic hepatitis. It combines a generic component, derived from the well-validated Short Form-36 Health Survey (SF-36), with hepatitis-specific domains that capture the unique impact of the disease and its treatment on patients' lives (101, 102). The generic component includes the eight SF-36 domains, which assess physical functioning, role limitations due to physical problems, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. These domains provide a broad evaluation of overall health status and allow for comparisons with other populations and disease conditions. The disease-specific component of the HQLQ addresses aspects of health particularly relevant to hepatitis, such as hepatitis-related health distress, positive well-being, functional limitations associated with hepatitis, cognitive function, health perceptions, and overall quality of life. The HQLQ instrument has been validated for use in patients with CHD (103).

10.1.2 Data collection

10.1.2.1 EQ-5D-3L

EQ-5D-3L was administered at baseline and Weeks 24, 40, 48, 72, 96, 144 and follow-up Weeks 48 (Week 192) and 96 (Week 240) for the bulevirtide 2 mg arm (35). For the BSC arm, EQ-5D-3L was administered at baseline and Weeks 24, 40 and, 48 (35). In Table 32, the missingness is presented for each arm.

Table 32 Pattern of missing data and completion – EQ-5D-3L

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Bulevirtide 2mg arm				
Baseline	49	0 (0.0%)	49	49 (100.0%)
Week 24	49	1 (2.0%)	49	48 (98.0%)
Week 40	49	5 (10.2%)	49	44 (89.8%)
Week 48	49	2 (4.1%)	48	47 (97.9%)
Week 72	49	3 (6.1%)	48	46 (95.8%)
Week 96	49	2 (4.1%)	47	47 (100.0%)
Week 144	49	4 (8.2%)	45	45 (100.0%)
Week 192	49	14 (28.6%)	35	35 (100.0%)
Week 240	49	21 (42.9%)	28	28 (100.0%)
BSC arm				
Baseline	51	0 (0.0%)	51	51 (100.0%)
Week 24	51	4 (7.8%)	50	47 (94.0%)
Week 40	51	3 (5.9%)	50	48 (96.0%)
Week 48	51	1 (2.0%)	50	50 (100.0%)

Abbreviations: EQ-5D-3L = EuroQol 5-dimension, 3-level; HRQoL = health-related quality of life

Sources: (35)

10.1.2.2 EQ-VAS

EQ-VAS was administered at the same timepoints as the EQ-5D-3L, that is at baseline and Weeks 24, 40, 48, 72, 96, 144 and follow-up Weeks 48 (Week 192) and 96 (Week 240) for the bulevirtide 2 mg arm (35). In the BSC arm, EQ-VAS was administered at baseline and

Weeks 24, 40 and, 48 (35). In Table 33, the missingness at each time points are listed per arm.

Table 33 Pattern of missing data and completion – EQ-VAS

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Bulevirtide 2mg arm				
Baseline	49	1 (2.0%)	49	48 (98.0%)
Week 24	49	1 (2.0%)	49	48 (98.0%)
Week 40	49	5 (10.2%)	49	44 (89.8%)
Week 48	49	1 (2.0%)	48	47 (97.9%)
Week 72	49	3 (6.1%)	48	46 (95.8%)
Week 96	49	2 (4.1%)	47	47 (100.0%)
Week 144	49	5 (10.2%)	45	44 (97.8%)
Week 192	49	14 (28.6%)	35	35 (100.0%)
Week 240	49	22 (44.9%)	28	27 (96.4%)
BSC arm				
Baseline	51	0 (0.0%)	51	51 (100.0%)
Week 24	51	4 (7.8%)	50	46 (92.0%)
Week 40	51	3 (5.9%)	50	48 (96.0%)
Week 48	51	1 (2.0%)	50	50 (100.0%)

Abbreviations: EQ-VAS = EuroQol Visual Analogue Scale; HRQoL = health-related quality of life

Sources: (35)

10.1.2.3 FSS

FSS was administered at baseline and Weeks 24, 40, 48, 72, 96, 144 and follow-up Weeks 48 (Week 192) and 96 (Week 240) for the bulevirtide 2mg arm. In Table 34 the missingness is reported for each arm.

Table 34 Pattern of missing data and completion – FSS

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Bulevirtide 2mg arm				
Baseline	49	0 (0.00%)	49	49 (100.00%)
Week 24	49	2 (4.1%)	49	47 (95.92%)
Week 40	49	1 (2.0%)	49	48 (98.0%)
Week 48	49	1 (2.0%)	48	48 (100.00%)
Week 72	49	3 (6.1%)	48	46 (95.8%)
Week 96	49	2 (4.08%)	47	47 (100.00%)
Week 144	49	4 (8.16%)	45	45 (100.00%)
Week 192	49	14 (28.57%)	35	35 (100.00%)
Week 240	49	21 (42.86%)	28	28 (100.00%)
BSC arm				
Baseline	51	0 (0.0%)	51	51 (100.0%)
Week 24	51	4 (7.8%)	50	47 (94.0%)
Week 40	51	3 (5.9%)	50	48 (96.0%)
Week 48	51	1 (2.0%)	50	50 (100.0%)

Abbreviations: FSS = Fatigue Severity Scale; HRQoL = health-related quality of life

Sources: (35)

10.1.2.4 HQLQ

For HQLQ, the two generic health summary score, health distress, positive wellbeing scale, and the hepatitis specific domain's missingness is presented in the tables below. In Table 35 the missingness for the HQLQ Physical Component Summary is presented.

Table 35 Pattern of missing data and completion – HQLQ Physical Component Summary

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Bulevirtide 2mg arm				
Baseline	49	0 (0.0%)	49	49 (100.0%)
Week 24	49	1 (2.0%)	49	48 (98.0%)
Week 40	49	5 (10.2%)	49	44 (89.8%)
Week 48	49	2 (4.1%)	48	47 (97.9%)
Week 72	49	3 (6.1%)	48	46 (95.8%)
Week 96	49	3 (6.1%)	47	46 (97.9%)
Week 144	49	4 (8.2%)	45	45 (100.0%)
Week 192	49	16 (32.7%)	35	33 (94.3%)
Week 240	49	21 (42.9%)	28	28 (100.0%)
BSC arm				
Baseline	51	0 (0.0%)	51	51 (100.0%)
Week 24	51	5 (9.8%)	50	46 (92.0%)
Week 40	51	4 (7.8%)	50	47 (94.0%)
Week 48	51	2 (3.9%)	50	49 (98.0%)

Abbreviations: HRQoL = health-related quality of life

Sources: (35)

In Table 36 the missingness for the HQLQ Mental Component Summary is presented.

Table 36 Pattern of missing data and completion – HQLQ Mental Component Summary

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Bulevirtide 2mg arm				
Baseline	49	0 (0.0%)	49	49 (100.0%)
Week 24	49	1 (2.0%)	49	48 (90.0%)
Week 40	49	5 (10.2%)	49	44 (89.8%)
Week 48	49	2 (4.1%)	48	47 (97.9%)
Week 72	49	3 (6.1%)	48	46 (95.8%)
Week 96	49	1 (4.1%)	47	46 (100%)
Week 144	49	4 (8.2%)	45	45 (100.0%)
Week 192	49	16 (32.7%)	35	33 (94.3%)
Week 240	49	21 (42.9%)	28	28 (100.0%)
BSC arm				
Baseline	51	0 (0.0%)	51	51 (100.0%)
Week 24	51	5 (9.8%)	50	46 (94.0%)
Week 40	51	4 (7.8%)	50	47 (94.0%)
Week 48	51	2 (2.0%)	50	49 (100.0%)

Abbreviations: HRQoL = health-related quality of life

Sources: (35)

In Table 37 the missingness for the HQLQ Health Distress Scale is presented.

Table 37 Pattern of missing data and completion – HQLQ Health Distress Scale

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

	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Bulevirtide 2mg arm				
Baseline	49	0 (0.0%)	49	49 (100.0%)
Week 24	49	1 (2.0%)	49	48 (98.0%)
Week 40	49	5 (10.2%)	49	44 (89,8%)
Week 48	49	1 (2,00%)	48	48 (100.0%)
Week 72	49	3 (6,12%)	48	46 (95,83%)
Week 96	49	3 (6.1%)	47	46 (97.9%)
Week 144	49	4 (8.2%)	45	45 (100,00%)
Week 192	49	16 (32.7%)	35	33 (94.3%)
Week 240	49	21 (42.9%)	28	28 (100.0%)
BSC arm				
Baseline	51	1 (2.0%)	51	50(98.0%)
Week 24	51	5 (9.8%)	50	46 (92.0%)
Week 40	51	4 (7.8%)	50	47 (94.0%)
Week 48	51	2 (3.9%)	50	49 (98.0%)

Abbreviations: HRQoL = health-related quality of life

Sources: (35)

In Table 38 the missingness for the HQLQ Positive Wellbeing Scale is presented.

Table 38 Pattern of missing data and completion – HQLQ Positive Wellbeing Scale

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)

Bulevirtide 2mg arm				
Baseline	49	0 (0.0%)	49	49 (100.0%)
Week 24	49	2 (4.1%)	49	47 (959%)
Week 40	49	5 (10.2%)	49	44 (89.8%)
Week 48	49	1 (2.0%)	48	48 (100.0%)
Week 72	49	3 (6.1%)	48	46 (95.8%)
Week 96	49	3 (6.1%)	47	46 (97.9%)
Week 144	49	4 (8.2%)	45	45 (100.0%)
Week 192	49	14 (28.6%)	35	35 (100.0%)
Week 240	49	21 (42.9%)	28	28 (100.0%)
BSC arm				
Baseline	51	0 (0.0%)	51	51 (100.0%)
Week 24	51	4 (7.8%)	50	47 (94.0%)
Week 40	51	4 (7.8%)	50	47 (94.0%)
Week 48	51	2 (3.9%)	50	49 (98.0%)

Abbreviations: HRQoL = health-related quality of life

Sources: (35)

In Table 39 the missingness for the HQLQ Hepatitis-Specific Limitations Scale is presented.

Table 39 Pattern of missing data and completion – HQLQ Hepatitis-Specific Limitations Scale

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients “at risk” at time point X	Number of patients who completed (% of patients expected to complete)
Bulevirtide 2mg arm				
Baseline	49	0 (0.0%)	49	49 (100.0%)
Week 24	49	1 (2.0%)	49	48 (98.0%)

Week 40	49	5 (10.2%)	49	44 (89.8%)
Week 48	49	1 (2.0%)	48	48 (100.0%)
Week 72	49	4 (8.2%)	48	45 (93.8%)
Week 96	49	3 (6.1%)	47	46 (97.9%)
Week 144	49	4 (8.2%)	45	45 (100.0%)
Week 192	49	14 (28.6%)	35	35 (100.0%)
Week 240	49	21 (42.9%)	28	28 (100.0%)
BSC arm				
Baseline	51	0 (0.0%)	51	51 (100.0%)
Week 24	51	4 (7.8%)	50	47 (94.0%)
Week 40	51	4 (7.8%)	50	47 (94.0%)
Week 48	51	2 (3.9%)	50	49 (98.0%)

Abbreviations: HRQoL = health-related quality of life

Sources: (35)

In Table 40 the missingness for the HQLQ Hepatitis-Specific Health Distress Scale is presented.

Table 40 Pattern of missing data and completion – HQLQ Hepatitis-Specific Health Distress Scale

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Bulevirtide 2mg arm				
Baseline	49	0 (0.0%)	49	49 (100.0%)
Week 24	49	1 (2.0%)	49	48 (98.0%)
Week 40	49	5 (10.2%)	49	44 (89.8%)
Week 48	49	1 (2.0%)	48	48 (100.0%)
Week 72	49	4 (8.2%)	48	45 (93.8%)

Week 96	49	3 (6.1%)	47	46 (97.9%)
Week 144	49	6 (12.2%)	45	43 (95.6%)
Week 192	49	16 (32.7%)	35	33 (94.3%)
Week 240	49	21 (42.9%)	28	28 (100.0%)
BSC arm				
Baseline	51	0 (0.0%)	51	51 (100.0%)
Week 24	51	4 (7.8%)	50	47 (94.0%)
Week 40	51	4 (7.8%)	50	47 (94.0%)
Week 48	51	2 (3.9%)	50	49 (98.0%)

Abbreviations: HRQoL = health-related quality of life

Sources: (35)

10.1.3 HRQoL results

10.1.3.1 Danish EQ-5D-5L index scores (mapped from EQ-5D-3L)

The Danish EQ-5D-5L index scores were calculated from the EQ-5D-3L response collected in the MYR301 trial which were mapped to EQ-5D-5L (94) and valued using the Danish value set for EQ-5D-5L (95). The EQ-5D-5L index scores, commonly referred to as utilities, increased from the baseline level throughout the treatment period, both for the treatment and the comparator arm. EQ-5D-5L Index scores were slightly higher in the bulevirtide arm than in the BSC arm from baseline and onwards increasing slightly more than in the BSC arm, as shown in Table 33. Figure 19 shows that the mean change from baseline was comparable between arms until Week 48. After Week 48, only HRQoL results for the bulevirtide arm are shown, as patients in the BSC arm transitioned to bulevirtide 10 mg at week 48.

Table 41 HRQoL EQ-5D-5L summary statistics

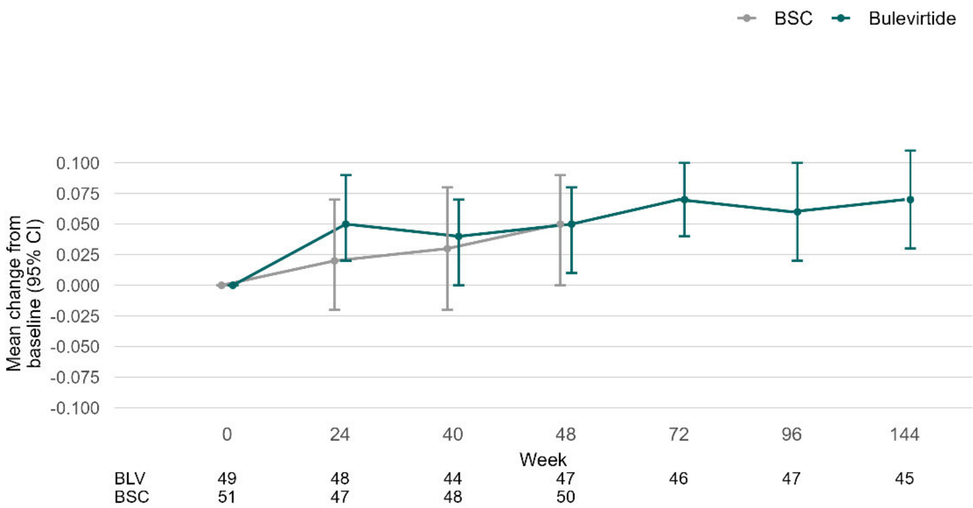
	Bulevirtide		BSC		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline	49	0.86 (0.02)	51	0.83 (0.02)	0.03 (-0.02 - 0.08); p value = 0.273
Week 24	48	0.92 (0.01)	47	0.85 (0.02)	0.07 (0.02 - 0.12); p-value = 0.009
Week 40	44	0.91 (0.02)	48	0.87 (0.02)	0.04 (-0.02 - 0.10); p-value = 0.177

Week 48	47	0.91 (0.01)	50	0.88 (0.02)	0.03 (-0.01 - 0.07); p-value = 0.180
Week 72	46	0.93 (0.01)	N/A	N/A	N/A
Week 96	47	0.93 (0.02)	N/A	N/A	N/A
Week 144	45	0.94 (0.02)	N/A	N/A	N/A

Abbreviations: EQ-5D-5L = EuroQol 5-dimension, 5-level; HRQoL = health-related quality of life; N/A = not applicable; NR = not reported

Sources: (104)

Figure 19 EQ-5D-5L index scores (mapped from EQ-5D-3L and valued with the DK value set) mean change from baseline



Mean change from baseline was calculated by subtracting the EQ-5D-5L index score (mapped from EQ-5D-3L to EQ-5D-5L and valued using the Danish value set for 5L) for each timepoint from the baseline value.

Sources: (35)

10.1.3.2 EQ-VAS scores

EQ-VAS scores were comparable at baseline. From baseline and onwards, the data showed a similar pattern as observed with the EQ-5D index scores with increases observed in both arms, numerically favouring the intervention as shown in Table 42 and in Figure 20. EQ-VAS score remained stable after planned treatment discontinuation after W144 in the bulevirtide arm, albeit with lower data availability. Beyond week 48, the HRQoL results are not shown, and patients in the BSC transitioned to bulevirtide treatment.

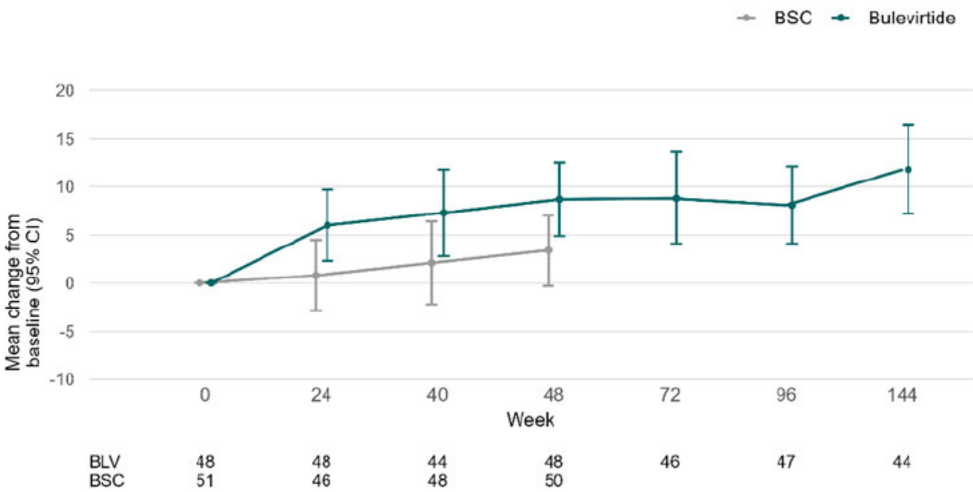
Table 42 HRQoL EQ-VAS summary statistics

	Bulevirtide		BSC		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline	48	73 (2.34)	51	72 (2.58)	1 (-5.82.7.82), p = 0.774
Week 24	48	79 (1.99)	46	73 (2.27)	6 (0.08.11.92), p = 0.047
Week 40	44	81 (2.08)	48	75 (2.97)	6 (-1.11.13.11), p = 0.098
Week 48	48	82 (1.49)	50	76 (2.59)	6 (0.15.11.85), p = 0.044
Week 72	46	81 (2.03)	N/A	N/A	N/A
Week 96	47	81 (1.94)	N/A	N/A	N/A
Week 144	44	86 (2.17)	N/A	N/A	N/A

Abbreviations: EQ-VAS = EuroQol Visual Analogue Scale; HRQoL = health-related quality of life; N/A = not applicable

Sources: (Gilead Sciences Inc. 2025a)

Figure 20 EQ-VAS mean change from baseline



Least squares (LS) means and 95% confidence intervals (CI) were from a MMRM model for change from baseline with treatment, visit, region, presence of cirrhosis, and treatment by visit interaction as fixed effects, and the baseline value as a covariate. Restricted maximum likelihoods (REML) was used to fit the model. Observed case (OC): missing values remain missing.

Sources: (Gilead Sciences Inc. 2025a)

10.1.3.3 FSS mean scores

FSS mean score showed a comparable development over time between the two arms. In the bulevirtide arm, the mean score remained relatively stable over all observable weeks. Beyond week 48, the HRQoL results are not shown for the BSC arm as patients in the BSC transitioned to bulevirtide treatment. The tabulated results are shown in Table 43 and the mean change from baseline in Figure 21.

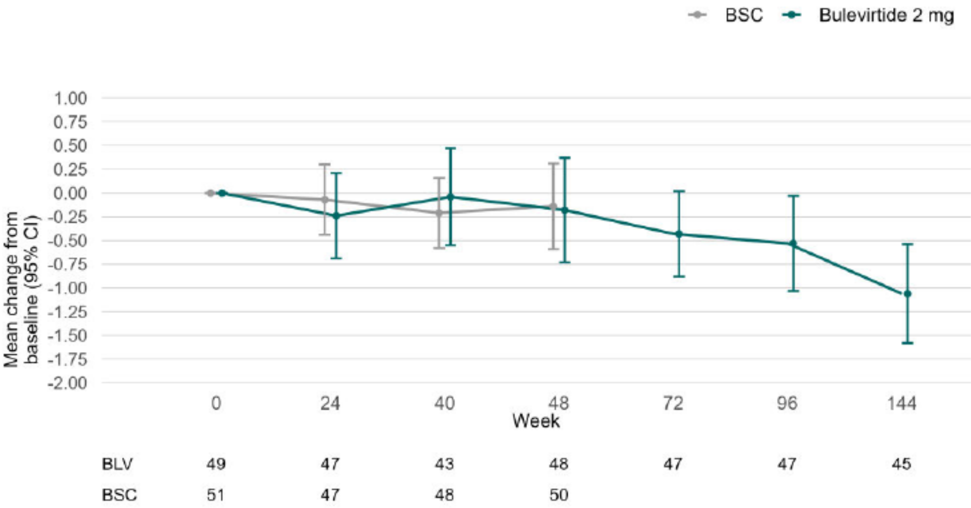
Table 43 HRQoL FSS mean score statistics

	Bulevirtide		BSC		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline	49	3.64 (0.23)	51	4.21 (0.22)	-0.57 (-1.20 - 0.06); p = 0.075
Week 24	47	3.41 (0.22)	47	4.25 (0.21)	-0.84 (-1.45 - -0.23); p = 0.007
Week 40	43	3.55 (0.23)	48	4.02 (0.23)	-0.47 (-1.11 – 0.17); p = 0.146
Week 48	48	3.50 (0.21)	50	4.14 (0.23)	-0.64 (-1,25 - -0.03); p = 0.039
Week 72	47	3.23 (0.20)	N/A	N/A	N/A
Week 96	47	3.17 (0.22)	N/A	N/A	N/A
Week 144	45	2.64 (0.20)	N/A	N/A	N/A

Abbreviations: E FSS = Fatigue Severity Scale; HRQoL = health-related quality of life; N/A = not applicable

Sources: (Gilead Sciences Inc. 2025a)

Figure 21 FSS mean score change from baseline



Least squares (LS) means and 95% confidence intervals (CI) were from a MMRM model for change from baseline with treatment, visit, region, presence of cirrhosis, and treatment by visit interaction as fixed effects, and the baseline value as a covariate. Restricted maximum likelihoods (REML) was used to fit the model. Observed case (OC): missing values remain missing.

Sources: (Gilead Sciences Inc. 2025a)

10.1.3.4 HQLQ summary and domain scores

In this section the two summary measurements of HQLQ, the Health Distress and the Positive Wellbeing scales, as well as the hepatitis specific components are presented. Beyond week 48, the HRQoL results are not shown for the BSC arm as patients in the BSC transitioned to bulevirtide treatment.

The result from the Physical Component Summary is presented in Table 44 and Figure 22. The scores are similar between the two arms while slightly, numerically, favouring the bulevirtide arm.

Table 44 HRQoL HQLQ Physical Component Summary score

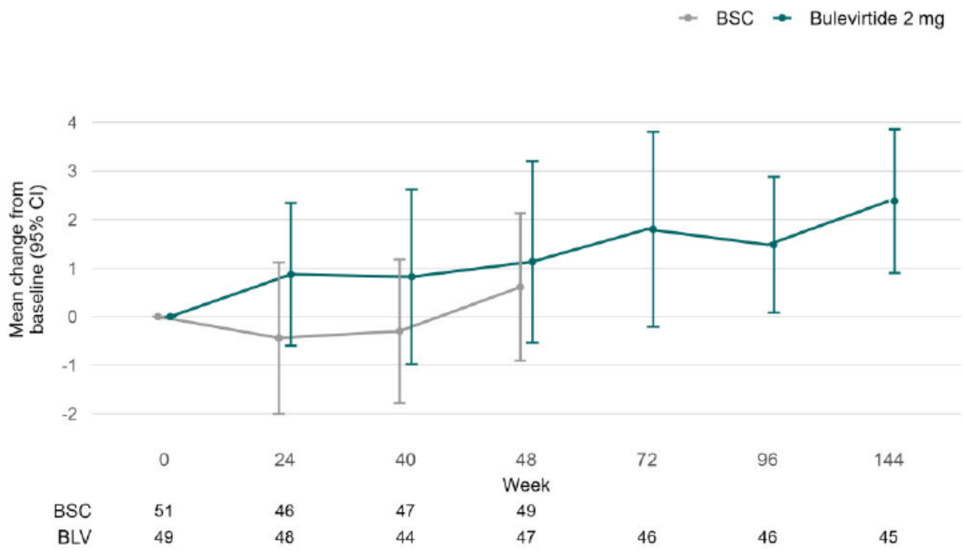
	Bulevirtide		BSC		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline	49	52.25 (0.81)	51	50.3 (1.05)	1.95 (-0.69 – 4.59); p-value = 0.145
Week 24	48	53.26 (0.77)	46	49.74 (1.00)	3.52 (1.00 - 6.04); p-value = 0.007

Week 40	44	53.49 (0.81)	47	50.03 (1.12)	3.46 (0.71 – 6.21); p-value = 0.014
Week 48	47	53.53 (0.84)	49	51.01 (1.02)	2.52 (-0.12 – 5.16); p-value = 0.061
Week 72	46	54.30 (0.92)	N/A	N/A	N/A
Week 96	46	54.00 (0.70)	N/A	N/A	N/A
Week 144	45	55.01 (0.77)	N/A	N/A	N/A

Abbreviations: E FSS = Fatigue Severity Scale; HRQoL = health-related quality of life; N/A = not applicable

Sources: (Gilead Sciences Inc. 2025a)

Figure 22 HQLQ Physical Component Summary score change from baseline



Least squares (LS) means and 95% confidence intervals (CI) were from a MMRM model for change from baseline with treatment, visit, region, presence of cirrhosis, and treatment by visit interaction as fixed effects, and the baseline value as a covariate. Restricted maximum likelihoods (REML) was used to fit the model. Observed case (OC): missing values remain missing.

Sources: (Gilead Sciences Inc. 2025a)

The result from the Mental Component Summary is presented in Table 45 and Figure 23. The scores are similar to the physical component with a slightly, numerically, favourable result in the bulevirtide arm.

Table 45 HRQoL HQLQ Mental Component Summary score

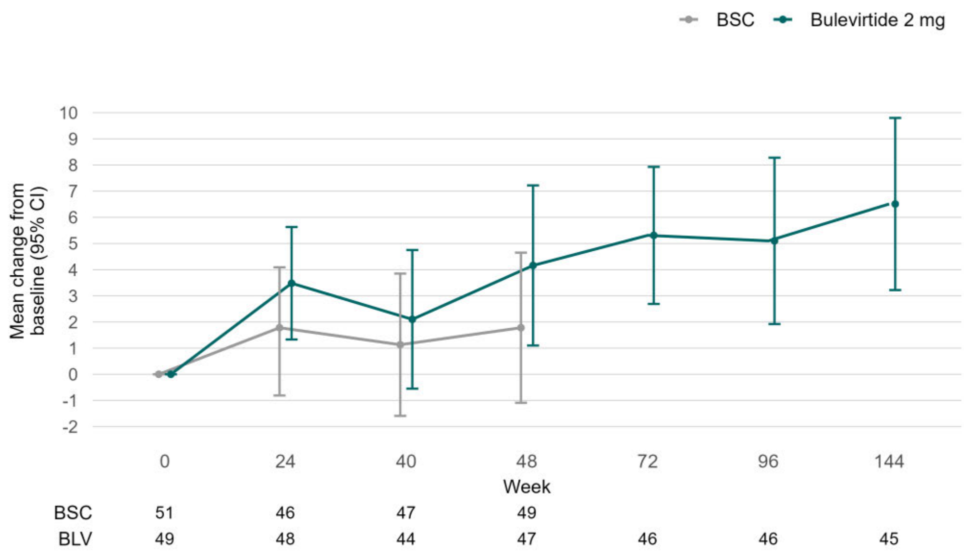
	Bulevirtide	BSC	Intervention vs. comparator

	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline	49	45.92 (1.45)	51	45.49 (1.41)	0.43 (-3.59 - 4.45); p-value = 0.832
Week 24	48	49.93 (1.10)	46	46.29 (1.52)	3.64 (-0.10 - 7.38); p-value = 0.056
Week 40	44	48.88 (1.31)	47	46.87 (1.55)	2.01 (-2.02 - 6.04); p-value = 0.324
Week 48	47	49.89 (1.16)	49	46.87 (1.36)	3.02 (-0.53 - 6.57); p-value = 0.094
Week 72	46	51.57 (1.12)	N/A	N/A	N/A
Week 96	46	51.71 (1.23)	N/A	N/A	N/A
Week 144	45	52.6 (1.31)	N/A	N/A	N/A

Abbreviations: E FSS = Fatigue Severity Scale; HRQoL = health-related quality of life; N/A = not applicable

Sources: (Gilead Sciences Inc. 2025a)

Figure 23 HQLQ Mental Component Summary score change from baseline



Least squares (LS) means and 95% confidence intervals (CI) were from a MMRM model for change from baseline with treatment, visit, region, presence of cirrhosis, and treatment by visit interaction as fixed effects, and the baseline value as a covariate. Restricted maximum likelihoods (REML) was used to fit the model. Observed case (OC): missing values remain missing.

Sources: (Gilead Sciences Inc. 2025a)

Table 46 and Figure 24 shows the scores from the Health Distress Scale. Consistent with the two summary components the two arms shows a similar pattern with numerically favourable results for the bulevirtide arm.

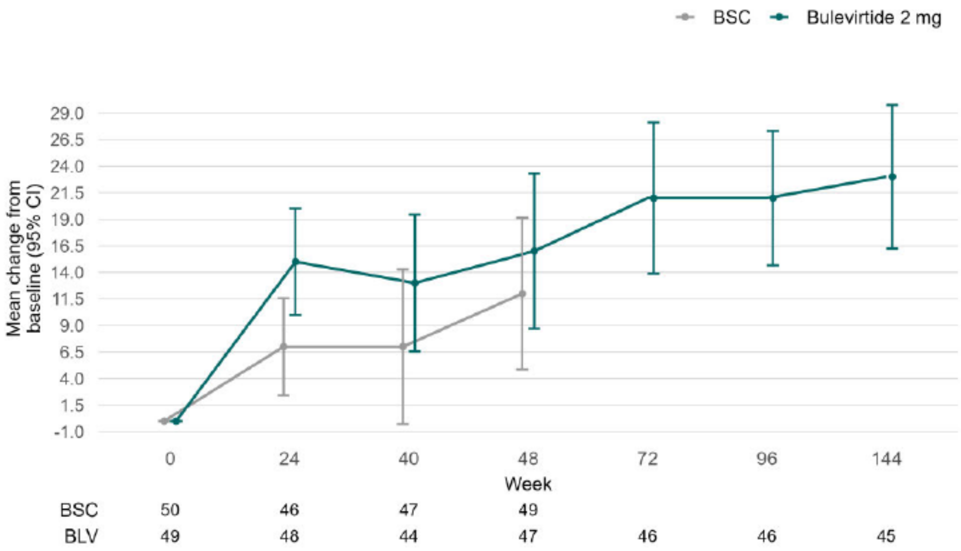
Table 46 HRQoL HQLQ Health Distress Scale score

	Bulevirtide		BSC		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline	49	61 (3.23)	50	58 (3.80)	3.00 (-6.91 - 12.91); p-value = 0.549
Week 24	48	77 (2.64)	46	63 (3.61)	14.00 (5.10 - 22.90); p-value = 0.002
Week 40	44	77 (3.29)	47	66 (3.81)	11.00 (1.00 - 21.00); p-value = 0.031
Week 48	47	78 (2.98)	49	69 (3.49)	9.00 (-0.10 - 18.10); p-value = 0.053
Week 72	46	82 (3.17)	N/A	N/A	N/A
Week 96	46	84 (2.34)	N/A	N/A	N/A
Week 144	45	86 (2.91)	N/A	N/A	N/A

Abbreviations: E FSS = Fatigue Severity Scale; HRQoL = health-related quality of life; N/A = not applicable

Sources: (Gilead Sciences Inc. 2025a)

Figure 24 HQLQ Health Distress Scale score change from baseline



Least squares (LS) means and 95% confidence intervals (CI) were from a MMRM model for change from baseline with treatment, visit, region, presence of cirrhosis, and treatment by visit interaction as fixed effects, and the baseline value as a covariate. Restricted maximum likelihoods (REML) was used to fit the model. Observed case (OC): missing values remain missing.

Sources: (Gilead Sciences Inc. 2025a)

The Positive Wellbeing score result is shown in Table 47 and Figure 25. Within this component the two arms show a similar pattern over time, while being stable in scores.

Table 47 HRQoL HQLQ Positive Wellbeing Scale score

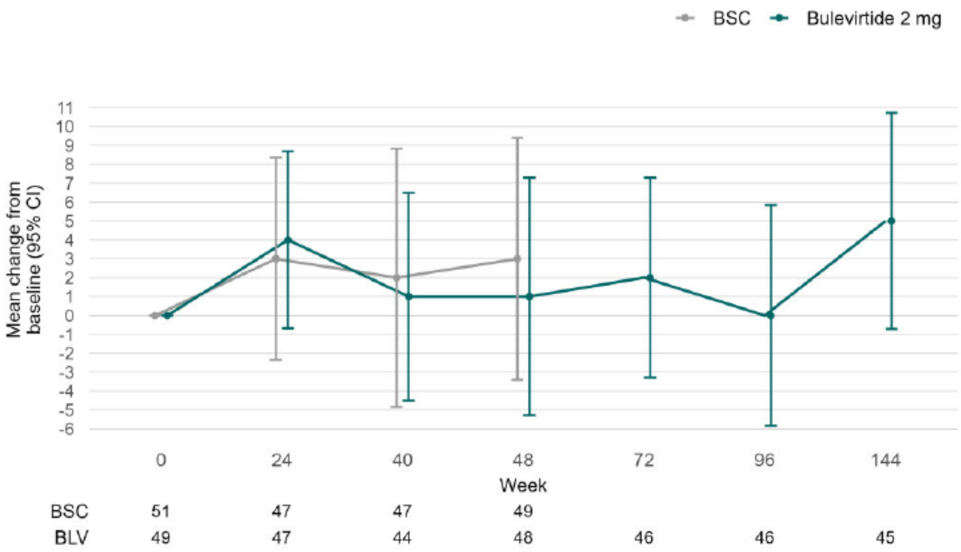
	Bulevirtide		BSC		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline	49	66 (2.74)	51	59 (3.14)	7.00 (-1.27 - 15.27); p-value = 0.096
Week 24	47	70 (2.96)	47	60 (3.08)	10.00 (1.52 - 18.48); p-value = 0.021
Week 40	44	67 (2.83)	47	60 (3.50)	7.00 (-1.95 - 15.95); p-value = 0.124
Week 48	48	67 (2.64)	49	61 (3.17)	6.00 (-2.20 - 14.20); p-value = 0.149
Week 72	46	68 (2.76)	N/A	N/A	N/A

Week 96	46	67 (2.67)	N/A	N/A	N/A
Week 144	45	72 (2.55)	N/A	N/A	N/A

Abbreviations: E FSS = Fatigue Severity Scale; HRQoL = health-related quality of life; N/A = not applicable

Sources: (Gilead Sciences Inc. 2025a)

Figure 25 HQLQ Positive Wellbeing score change from baseline



Least squares (LS) means and 95% confidence intervals (CI) were from a MMRM model for change from baseline with treatment, visit, region, presence of cirrhosis, and treatment by visit interaction as fixed effects, and the baseline value as a covariate. Restricted maximum likelihoods (REML) was used to fit the model. Observed case (OC): missing values remain missing.

Sources: (Gilead Sciences Inc. 2025a)

The result from the Hepatitis-Specific Limitations Scale is presented in Table 48 and Figure 26. The scores are similar between the two arms while slightly, numerically, favouring the bulevirtide arm.

Table 48 HRQoL HQLQ Hepatitis-Specific Limitations Scale score

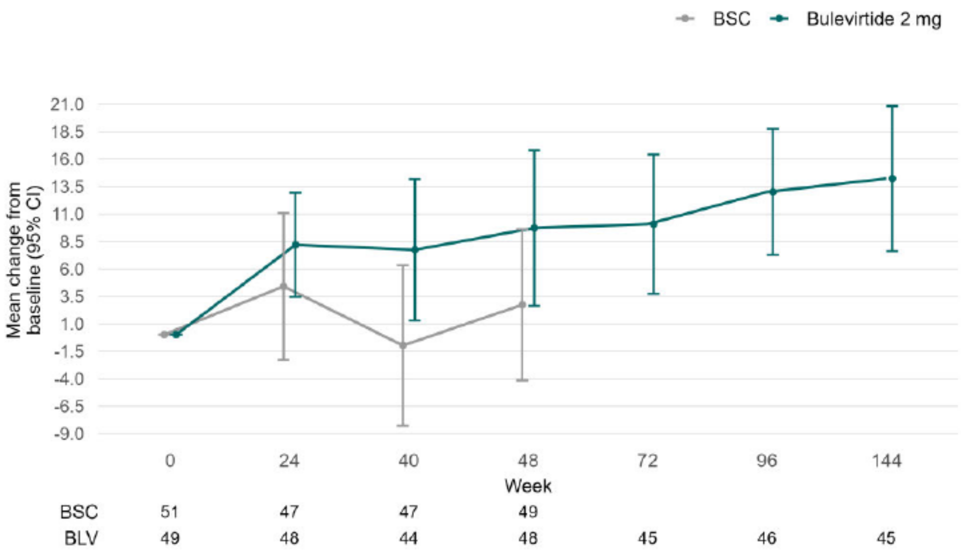
	Bulevirtide		**BSC**		**Intervention vs. comparator**
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline	49	75.78 (3.55)	51	70.59 (4.02)	5.19 (-5.45 - 15.83); p-value = 0.336
Week 24	48	84.86 (2.64)	47	76.31 (3.43)	8.55 (-0.06 - 17.16); p-value = 0.052

Week 40	44	85.3 (2.93)	47	72.77 (4.11)	12.53 (2.49 - 22.57); p-value = 0.015
Week 48	48	85.42 (2.42)	49	76.19 (3.72)	9.23 (0.40 - 18.06); p-value = 0.041
Week 72	45	86.07 (3.01)	N/A	N/A	N/A
Week 96	46	92.59 (1.90)	N/A	N/A	N/A
Week 144	45	90.96 (2.41)	N/A	N/A	N/A

Abbreviations: E FSS = Fatigue Severity Scale; HRQoL = health-related quality of life; N/A = not applicable

Sources: (Gilead Sciences Inc. 2025a)

Figure 26 HQLQ Hepatitis-Specific Limitations Scale score change from baseline



Least squares (LS) means and 95% confidence intervals (CI) were from a MMRM model for change from baseline with treatment, visit, region, presence of cirrhosis, and treatment by visit interaction as fixed effects, and the baseline value as a covariate. Restricted maximum likelihoods (REML) was used to fit the model. Observed case (OC): missing values remain missing.

Sources: (Gilead Sciences Inc. 2025a)

In Table 49 and Figure 27 the Hepatitis-Specific Health Distress score is shown. The scores of the component numerically favours the bulevirtide arm. Noticeably, the score keeps increasing over time without any visible plateau observed.

Table 49 HRQoL HQLQ Hepatitis-Specific Health Distress score

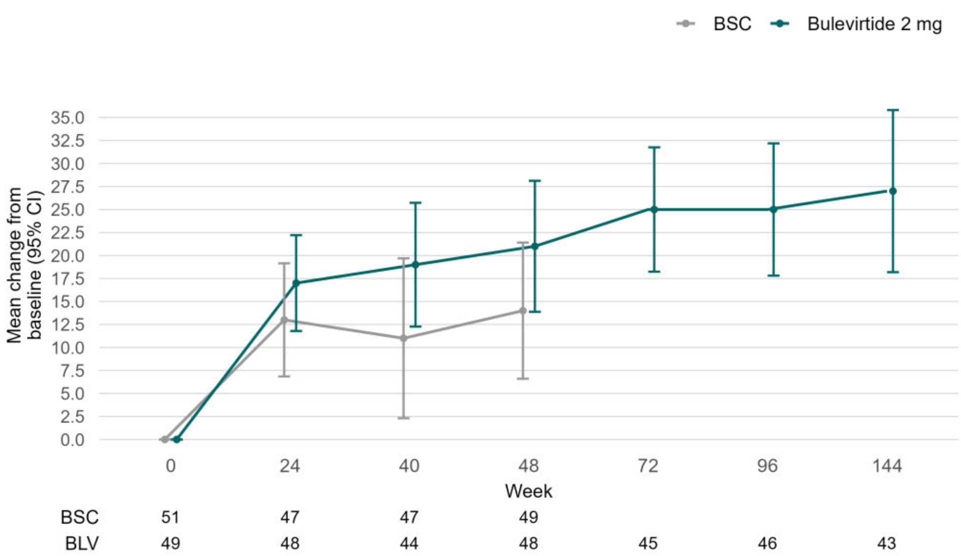
	Bulevirtide	BSC	Intervention vs. comparator

	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline	49	56 (3.74)	51	52 (4.20)	4.00 (-7.17 - 15.17); p-value = 0.479
Week 24	48	74 (3.15)	47	63 (4.42)	11.00 (0.21 - 21.79); p-value = 0.046
Week 40	44	77 (3.27)	47	63 (4.59)	14.00 (2.78 - 25.22); p-value = 0.015
Week 48	48	77 (3.12)	49	65 (3.83)	12.00 (2.19 - 21.81); p-value = 0.017
Week 72	45	81 (3.25)	N/A	N/A	N/A
Week 96	46	82 (3.17)	N/A	N/A	N/A
Week 144	43	83 (3.37)	N/A	N/A	N/A

Abbreviations: E FSS = Fatigue Severity Scale; HRQoL = health-related quality of life; N/A = not applicable

Sources: (Gilead Sciences Inc. 2025a)

Figure 27 HQLQ Hepatitis-Specific Health Distress score change from baseline



Least squares (LS) means and 95% confidence intervals (CI) were from a MMRM model for change from baseline with treatment, visit, region, presence of cirrhosis, and treatment by visit interaction as fixed effects, and the baseline value as a covariate. Restricted maximum likelihoods (REML) was used to fit the model. Observed case (OC): missing values remain missing.

Sources: (Gilead Sciences Inc. 2025a)

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

10.2.1 HSUV calculation

The DK value set for EQ-5D-5L was used to calculate utilities (i.e. EQ-5D index scores) based on the EQ-5D data collected in the MYR301 trial (EQ-5D-3L collected and mapped to EQ-5D-5L). In the bulevirtide 2mg arm responses were collected at baseline and weeks 24, 40, 48, 72, 96, 144, follow-up Weeks 48 (Week 192) and 96 (Week 240). For the BSC arm at baseline, weeks 24, 40, 48, respectively. To inform the model health states, biopsy results are needed to associate HRQoL to fibrosis. In line with the study protocol biopsies were only collected during the treatment period at baseline and week 48. Furthermore, biopsies were not mandatory but voluntary and thus the observations reporting both EQ-5D and biopsy results are fewer than the reported completeness in Table 32. Data from the clinical trial allowed for population of utility values for health states F0 to F4. The number of respondents used to calculate the health state values are shown in Table 50.

Table 50 Number of patients by health state and response status

Health State[a]	Combined responder	N (responses)	n (respondents)
F0	No	14	13
F0	Yes	6	6
F1	No	36	32
F1	Yes	4	4
F2	No	34	30
F2	Yes	4	4
F3	No	11	10
F3	Yes	1	1
F4	No	2	1
F4	Yes	1	1
NA	No	77	46
NA	Yes	7	7

[a] = individuals without biopsy (and therefore without F-stage) are listed as NA in the table.

Abbreviations: F0-4 = fibrosis stage 0-4; BSC = best supportive case; NA = Not available

Sources: (104)

Utilities associated with the different health states in the model reflect the impact of disease progression on a patients' quality of life and thus HSUV values were calculated by health state (HS) and responder status using a mixed model for repeated measures (MMRM) approach. The sample size for the analysed population consisted of 47 patients in the bulevirtide arm, and 50 patients in the BSC arm summing to a total of 97 patients with 197 observations. From the original set, 84 observations were discarded from the analysis due to lack of biopsy data. The model was fitted with the fixed effects: baseline utility, health state, and combined response. The coefficients are presented in Table 34.

Table 51 coefficients from the MMRM model informing health state utilities in the health economic analysis

	Estimate	Std. Error	t value	Pr(>|t|)
(Intercept)	0.428	0.073	5.898	0.000
Baseline score	0.577	0.077	7.497	0.000
Health state F0 (reference category)	-	-	-	-
Health state F1	-0.047	0.025	-1.863	0.065
Health state F2	-0.065	0.026	-2.527	0.013
Health state F3	-0.037	0.035	-1.048	0.297
Health state F4	-0.079	0.056	-1.392	0.167
Combined response	0.041	0.025	1.613	0.110

Abbreviations: F0-4 = fibrosis stage 0-4

Sources: (104)

The model equation is specified as:

$$Health\ state\ utility_{it} = \beta 0 + \beta 1 \times Baseline_i + \beta 2 \times HealthState_{it} + \beta 3 \times CR_{it} + \varepsilon_{it}$$

Where ε_{it} is the error term.

In the model HSUV have been age adjusted in line with the DMC's methods guide (105).

10.2.1.1 Mapping

For this analysis, the EQ-5D-3L was mapped to EQ-5D-5L by means of a validated mapping method (94). The mapping was done according to the preferred method which was an ordinal logistic regression that disregarded age and gender and accounted for unobserved heterogeneity using a latent factor. The same mapping has previously been applied and accepted in submission to the DMC (106-108).

10.2.2 Disutility calculation

No disutilities were calculated from the clinical trial, but a utility correction for the patients that discontinued treatment due to achieving the stopping rule of undetectable HDV RNA, described in section 8.4, was added by request from the DMC. The size of the utility correction is modelled as the same size as the difference between responders and non-responders. The correction is added to the same cycle as the patients relapses and is implemented for that proportion for one cycle, as those who relapse while off therapy regain treatment response within 24 weeks when BLV treatment has been reinitiated.(91, 92).

Table 52 Relapsing patient utility correction

Correction factor size	Applied to	Duration	Source
0.041	Relapsing patients	One cycle	DMC request

10.2.3 HSUV results

Utilities associated with the different health states in the model are a reflection of the impact of disease progression on a patients' quality of life. The model allows for differentiation of quality of life between responders, suboptimal responders, and non-responders. In this application responders and non-responders are used. The model's ability to input values for suboptimal responders serves as a placeholder as currently there is no data to model the clinical benefit of suboptimal responder but can be populated when such data is available. In the model, no difference is assumed between non-responders and suboptimal responders, and the input values for suboptimal responders are currently set to the utility values of the non-responders. Health utility values and disutility values are shown in Table 35. As shown in Table 34, there is a difference of 0.041 (-0.008 – 0.090) for fibrosis stages (F0-F3) and for the compensated cirrhosis (F4) between the responder and non-responder utility values used to differentiate between these two populations in the model (109).

Table 53 Overview of health state utility values

	Results [95%CI][a]	Instrument	Tariff (value set) used	Comments
Non-Responders, and Suboptimal Responders				
F0	0.918 (0.875 - 0.961)	EQ-5D-3L mapped to 5L	DK	Predicted values using the MMRM model for week 48 covariates
F1	0.871 (0.842 - 0.900)			

F2	0.853 (0.824 - 0.883)			
F3	0.881 (0.828 - 0.934)			
F4 (CC)	0.840 (0.734 - 0.945)			
Responders				
F0	0.959 (0.906 - 1)	EQ-5D-3L mapped to 5L	DK	Predicted values using the MMRM model for week 48 covariates
F1	0.912 (0.859 - 0.964)			
F2	0.894 (0.842 - 0.947)			
F3	0.922 (0.851 - 0.993)			
F4 (CC)	0.881 (0.772 - 0.989)			

[a] 95% CIs calculated using the variance-covariance matrix of MMRM parameter estimates, assuming asymptotic normality

Abbreviations: CC = compensated cirrhosis; DCC = decompensated cirrhosis; DK = Denmark; EQ-5D-5L = EuroQol 5-dimension, 5-level; EQ-5D-3L = EuroQol 5-dimension, 3-level; F1-4 = fibrosis stage 1-4; HCC = hepatocellular carcinoma; HSUV = health state utility value; LT = liver transplant; PLT = post-liver transplant.

Sources: (104)

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

10.3.1 Study design

10.3.1.1 HSUV

Utility values for the severe liver disease health states were sourced from the publications identified via SLR by Kaushik et al. (71). For this submission the two studies by Scalone et al. (72)and Björnsson et al. (73)have been used. These two publications were chosen based on their use of EQ-5D-3L with UK tariff and based on their coverage of the different health states and sample size.

10.3.1.2 Disutilities

Adverse events included in the health economic model were based on the observed incidence in the MYR301 trial. Disutilities were applied as a one-time disutility at the start of treatment, i.e. applied in the first cycle in the model. To best represent the Danish population values for the adverse events were sourced from Hvidberg et al. (75), a compilation of EQ-5D-3L Health-Related Quality-of-Life scores for chronic conditions and health risks. While being 3L and not 5L this was determined to be the most appropriate source among the available options, being country specific.

10.3.2 Data collection

10.3.2.1 HSUV

The SLR of Kaushik et al. identified a total of 24 studies meeting the inclusion criteria for the meta-analysis defined in the study (71). The SLR found no studies reporting utility values for hepatitis D and therefore utility values for hepatitis B and hepatitis C have been used as proxies for hepatitis D.

For this submission two studies were chosen based on them reporting EQ-5D-3L utilities using the UK tariff and based on that these studies had the largest sample size.

The majority of the severe liver disease health states was covered by Scalone et al. (HCC and PLT) (72). The health state DCC was sourced from Björnsson et al. (73).

The LT health state was sourced by scaling the PLT utility value from Scalone et al. with the relationship for PLT year 1 and PLT year 2 from the hepatitis B any instrument meta-analysis presented in table 3 in Kaushik et al. (LT = PLT * (0.57/0.67)) (71).

The above UK tariff EQ-5D-3L health state utilities were mapped to Danish tariff EQ-5D-5L utilities using the algorithm described by Torkilseng et al. (76). The algorithm was developed using patient-level data from 11 oncology trials and validated on an external dataset consisting of three clinical trials with the largest absolute prediction error of 0.020 for the best fitting model. Earlier research on comparable methods suggest that such algorithms are robust regardless of disease area of the source data, and the disease area in which they are applied (111).

The best fitting model, an ordinary least squares regression model, was selected based on Akaike Information Criteria resulting in the following mapping algorithm between EQ-5D-3L utility UK tariff values to Danish tariff EQ-5D-5L values:

$$mean\ Danish\ EQ\_5D\_5L = 0.231 + 0.773 * mean\ UK\ EQ\_5D\_3L$$

10.3.2.2 Disutilities

Hvidberg et al. (75) combined 55,616 respondents from 3 national health survey samples which were pooled and combined with 7 national registers containing patient-level information on diagnoses, health care activity, and socio-demographics. EQ-5D-3L data were converted to utility scores using the Danish EQ-5D-3L value set to estimate the mean utility for each chronic disease population. Adjusted limited dependent variable mixture models were estimated and used to provide a regression-based catalogue of utilities and disutilities.

The adverse events in the health economic model were matched based on ICD-10 code to the most appropriate item within the catalogue.

10.3.3 HRQoL Results

10.3.3.1 HSUV results

Utility values for the HS are shown in Table 36. As noted above, disease progression to DCC or HCC triggers the treatment stopping rule; therefore, liver disease health state utility values do not vary by responder status for these health states.

Table 54 Overview of health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
DCC	0.738 (0.681 – 0.795)	EQ-5D-5L	DK	Mean value 0.656 (DCC, EQ-5D-3L) from Björnsson et al.(73), mapped to DK value by Torkilseng et al. (76)
HCC	0.816 (0.762 – 0.871)	EQ-5D-5L	DK	Mean value 0.757 (HCC, EQ-5D-3L) from Scalone et al. (72), mapped to DK value by Torkilseng et al. (76)
LT	0.701 (0.672 – 0.730)	EQ-5D-5L	DK	Mean value 0.767 (PLT, EQ-5D-3L) from Scalone et al.(72), mapped to DK value by Torkilseng et al. (76), multiplied by relationship of PLT(Y1) and PLT(Y2) (cHBV, any instrument) from Kaushik et al. (71)
PLT	0.824 (0.789 – 0.858)	EQ-5D-5L	DK	Mean value 0.767 (PLT, EQ-5D-3L) from Scalone et al.(72), mapped to DK value by Torkilseng et al. (76)

Abbreviations: DCC = decompensated cirrhosis; HCC = hepatocellular carcinoma; HSUV = health state utility value; LT = liver transplant; PLT = post-liver transplant.; DK = Denmark; EQ-5D-5L = EuroQol 5-dimension, 5-level

10.3.3.2 Disutilities results

Disutility values for each occurrence of an adverse event are presented in Table 37 and sourced from (75). The disutility value for neutropenia, leukopenia, and thrombocytopenia are assumed to have the same impact as for other blood disorders. Disutility values were applied one-off at the beginning of the model. As disutility values were presented separately for genders the average was used as the model input.

Table 55 Overview of literature-based AE-disutilities

	Results	Instrument	Tariff (value set) used	Comments

	[95% CI]			
Neutropenia	0.014 [NR]	EQ-5D-3L	DK	Table 4, Item 24, ICD-10: D70-D77, Hvidberg et al. (75). Disutility was calculated as the average of male and female.
Thrombocytopenia	0.014 [NR]	EQ-5D-3L	DK	Table 4, Item 24, ICD-10: D70-D77, Hvidberg et al. (75). Disutility was calculated as the average of male and female.
Leukopenia	0.014 [NR]	EQ-5D-3L	DK	Table 4, Item 24, ICD-10: D70-D77, Hvidberg et al. (75). Disutility was calculated as the average of male and female.

Abbreviations: DK = Denmark; EQ-5D-3L = EuroQol 5-dimension, 3-level; NR: Not reported

11. Resource use and associated costs

11.1 Medicines - intervention and comparator

Patients on bulevirtide receive a daily dose of 2 mg. The pharmacy purchase price per package containing 30 vials of 2 mg each is 52 632 DKK (112). Since the recommended treatment dose is a fixed dose of one vial, waste and vial sharing is not relevant. Since BSC for HDV does not include any active treatment, no drug acquisition costs are included for patients on BSC only (Section 3.5).

Table 56 Medicines used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Bulevirtide	2 mg	100%	Daily	No

11.2 Medicines– co-administration

Not applicable.

11.3 Administration costs

Bulevirtide is given in daily subcutaneous injections. Patients will be instructed to self-administer the drug at home, as daily administrations at the hospital will be unfeasible and unnecessary for the vast majority of patients. Step-by-step instructions for self-administration are also included in the drug package. As self-administrations, once the patient has learnt to self-administer, do not carry an additional healthcare cost, only outpatient visits at treatment initiation including training in self-administration is included as administration cost. The mean number of visits required to learn to self-administer was sourced from a Nordic clinical expert (39).

Table 57 Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
Subcutaneous (outpatient visit at treatment initiation incl. training in self-administration)	4 visits	2001.00	Diagnosekode: (DB180) Kronisk viral hepatitis B med Delta agens Varighed: <12 hours 07MA98 MDC07 1-dagsgruppe, pat. mindst 7 år	DRG 2026 (39)

Abbreviations: DKK = Danish krona

11.4 Disease management costs

Disease management costs are divided between three categories:

- Disease management in hospital costs
- Disease monitoring costs which differ between patient on and off treatment
- One-off disease management costs for the non-requiring event of liver transplantation

For patients in the DCC state, HCC state and PLT state, the cost of disease management in hospital are included based on health state. The unit costs were sourced using DRG. The visit frequencies for patients in DCC and HCC were sourced from Lidgren, Hollander (82) and the corresponding for patients in PLT was sourced from Nguyen, Burak Ozbay (113). The cost of disease management in hospital are presented in Table 40.

Table 58 Disease management costs used in the model: disease management in hospital

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Outpatient visit (DCC)	Every 2 months	2001.00	Diagnosekode: (DB180) Kronisk viral hepatitis B med Delta agens Varighed: <12 hours	Unit cost: DRG 2026 Frequency: Lidgren et al. (82)

			07MA98 MDC07 1-dagsgruppe, pat. mindst 7 år	
Inpatient visit (DCC)	Every 6 months	41 017.00	Diagnosekode: (DB180) Kronisk viral hepatitis B med Delta agens Varighed: ≥12 hours 07MA05 Kronisk leversygdom uden komplikationer	Unit cost: DRG 2026 Frequency: Lidgren et al. (82)
Outpatient visit (HCC)	Every 3 months	2001.00	Diagnosekode: (DB180) Kronisk viral hepatitis B med Delta agens Varighed: <12 hours 07MA98 MDC07 1-dagsgruppe, pat. mindst 7 år	Unit cost: DRG 2026 Frequency: Lidgren et al. (82)
Inpatient visit (HCC)	Every 4 months	47 233.00	Diagnosekode: (DC220) Hepatocellulært karcinom Varighed: ≥12 hours 07MA08 Ondartede sygdomme i lever, galdeveje og bugspytkirtel, pat. mindst 18 år	Unit cost: DRG 2026 Frequency: Lidgren et al. (82)
Outpatient visit (PLT)	Every 3 months	2001.00	Diagnosekode: (DB180) Kronisk viral hepatitis B med Delta agens Varighed: <12 hours	Unit cost: DRG 2026 Frequency: Nguyen et al. (113)

			07MA98 MDC07 1-dagsgruppe, pat. mindst 7 år	
Inpatient visit (PLT)	Every 9 months	71 021.00	Diagnosekode: (DZ944) Levertransplanteret Varighed: ≥12 hours 07MA01 Tilstand med transplanteret lever	Unit cost: DRG 2026 Frequency: Nguyen et al. (113)

Abbreviations: DCC = decompensation cirrhosis; HCC = hepatocellular carcinoma; PLT = post-liver transplant

For F0-F4, disease management in hospital was not included, as per Lidgren, Hollander (82) as this is a part of the disease monitoring costs. The model additionally includes monitoring costs in the form of outpatient visits which include the costs of paraclinical tests assumed to be handled in conjunction with the visits. The frequency of events was distinguished between during treatment and off-treatment (relevant to BSC arm, and bulevirtide patients off treatment) and further divided into event frequencies for patients without CC (NC, i.e. F0-F3) and CC (i.e. F4). Visit frequencies were informed by a Nordic clinical expert (39) (Table 41).

Table 59 Disease management costs used in the model: monitoring on and off treatment

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
On treatment				
Outpatient visit (F0-F3)	Every 2 months	2001	Diagnosekode: (DB180) Kronisk viral hepatitis B med Delta agens Varighed: <12 hours 07MA98 MDC07 1-dagsgruppe, pat. mindst 7 år	DRG 2026 (39)
Outpatient visit (F4)	Every 1.5 months	2001	Diagnosekode: (DB180) Kronisk viral hepatitis B med Delta agens Varighed: <12 hours 07MA98 MDC07 1-dagsgruppe, pat. mindst 7 år	DRG 2026 (39)

Off treatment

Outpatient visit (F0-F3)	Every 6 months	2001	Diagnosekode: (DB180) Kronisk viral hepatitis B med Delta agens Varighed: <12 hours 07MA98 MDC07 1-dagsgruppe, pat. mindst 7 år	DRG 2026 (39)
Outpatient visit (F4)	Every 2 months	2001	Diagnosekode: (DB180) Kronisk viral hepatitis B med Delta agens Varighed: <12 hours 07MA98 MDC07 1-dagsgruppe, pat. mindst 7 år	DRG 2026 (39)

Abbreviations: DKK = Danish krona; F0-4 = fibrosis stage 0-4; NC: Non-cirrhotic; CC: Compensated cirrhosis

The liver transplant cost is a one-off cost amounting to 932 526 DKK (Table 42).

Table 60 One-off disease management costs used in the model

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Liver transplant	One-off	932 526.00	Procedurekode: (KJJC00) Allogen levertransplantation 26MP06 Levertransplantation	DRG 2026

Abbreviations: DKK = Danish krona

11.5 Costs associated with management of adverse events

The model includes AEs as measured in the MYR301 trial. The frequencies of the AEs are presented in Section 9. The unit cost for each adverse event has been sourced using DRG and are shown in Table 43 (114). Outpatient stays for the treatment of the included AEs are used as bulevirtide is generally perceived to be very well tolerated (39). Adverse event costs were applied as one-time costs in the first cycle at the start of the treatment.

Table 61 Cost associated with management of adverse events

	DRG code	Unit cost
Neutropenia	Diagnosekode: (DB180) Kronisk viral hepatitis B med Delta agens and (DD709) Neutropeni UNS	2001 DKK (114)

	Varighed: <12 hours DRG 07MA98 MDC07 1-dagsgruppe, pat. mindst 7 år	
Thrombocytopenia	Diagnosekode: (DB180) Kronisk viral hepatitis B med Delta agens and (DD709) Trombocytopeni UNS Varighed: <12 hours DRG 07MA98 MDC07 1-dagsgruppe, pat. mindst 7 år	2001 DKK (114)
Leukopenia	Diagnosekode: (DB180) Kronisk viral hepatitis B med Delta agens and (DD729) Sygdom i hvide blodlegemer UNS Varighed: <12 hours DRG 07MA98 MDC07 1-dagsgruppe, pat. mindst 7 år	2001 DKK (114)

Abbreviations: DKK = Danish krona

11.6 Subsequent treatment costs

No subsequent treatments are included in the model since there are no other treatments available for this group of patients who are ineligible for pegIFN-α or who have already attempted pegIFN-α.

Table 62 Medicines of subsequent treatments

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
[Name of the intervention]	[E.g. 5 mg]	[E.g. 97 %]	[E.g. every second week]	[Yes/no]
[Name of the comparator]	[E.g. 5 mg]	[E.g. 97 %]	[E.g. every second week]	[Yes/no]

11.7 Patient costs

Costs due to patient time and transportation are included in the analysis for visits in relation to treatment administration and disease management. For all events, a two-way travel is included. In addition, for all outpatient visits, one hour of patient time is assumed. For inpatient visits for patients with decompensated cirrhosis, 5 days per stay is included, based on Lidgren, Hollander (82). The corresponding for patients with hepatocellular carcinoma, as well as in association with liver transplantation and inpatient visits in the post-transplant state is 7 days (82). It is worth mentioning that in Lidgren, Hollander (82) the patient time for transplantation (7 days) is presented as “Other inpatient admissions including laboratory tests”. This data was used since no more accurate data was identified. Unit costs for patient time (188 DKK/h) and transportation (two-way, 140 DKK) are derived from DMC (115).

Table 63 Patient costs used in the model

Activity	Time spent [minutes, hours, days]
<u>**Administration**</u>	
Outpatient visit at treatment initiation incl. training in self-administration	1 h/event; 1 two-way-travel/event (based on assumption)
<u>**Disease managament**</u>	
Outpatient visit	1 h/event; 1 two-way-travel/event (based on assumption)
Inpatient visit (Decompensated cirrhosis)	5 days à 16 hours/event; 1 two-way-travel/event Lidgren et al. (82)
Inpatient visit (Hepatocellular carcinoma)	7 days à 16 hours /event; 1 two-way travel/event Lidgren et al. (82)
Inpatient visit (Post-liver transplant)	7 days à 16 hours /event; 1 two-way travel/event Lidgren et al. (82)
Liver Transplantation	7 days à 16 hours /event; 1 two-way travel/event Lidgren et al. (82)

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

Not applicable.

12. Results

12.1 Base case overview

Table 46 shows the base case settings of the health economic model.

Table 64 Base case overview

Feature	Description
Comparator	BSC only
Type of model	Decision tree followed by a Markov model
Time horizon	64 years (life time)

Treatment line	Patients in fibrosis stages F2 or F3 who are ineligible for pegIFN-α (1L) or who have already attempted pegIFN-α treatment without effect (2L), or patients who are cirrhotic (1 or 2L)
Measurement and valuation of health effects	The EQ-5D-3L responses from MYR301 were mapped to EQ-5D-5L and valued with the Danish EQ-5D-5L value set to obtain the EQ-5D-5L index scores required to inform the health economic model.
Costs included	Medicine costs Disease management costs Adverse event costs Patient costs
Dosage of medicine	2 mg daily
Average time on treatment (years)	Intervention: 10.21 Comparator: N/A

Abbreviations: BSC = best supportive care; N/A = not applicable; F0 = fibrosis stage 0; F1 = fibrosis stage 1; F2 = fibrosis stage 2; F3 = fibrosis stage 3; F4 = fibrosis stage 4; DCC = decompensated cirrhosis, HCC = hepatocellular carcinoma; LT = liver transplant; PLT post-liver transplant

12.1.1 Base case results

The base case results, shown in Table 47, shows that bulevirtide is more costly (3 978 241 DKK) but also more effective (4.36 QALYs) than BSC only. The resulting incremental cost effectiveness ratio (ICER) is 912 105 DKK. The drug acquisition cost constitutes the largest difference in costs. QALY gains almost exclusively arise from patients spending more time in the less severe health states, while the impact of AEs is negligible. In addition, the intervention prolongs life with 4.67 years.

Table 65 Base case results, discounted estimates

	Bulevirtide	BSC only	Difference
Medicine costs	3 992 337	0	3 992 337
Medicine costs – co-administration	0	0	0
Administration	**7 658**	**0**	7 658
Disease management costs	220 079	240 665	-20 587
Costs associated with management of adverse events	**18**	**104**	-86

Subsequent treatment costs	0	0	0
Patient costs	67 734	68 816	-1 081
Palliative care costs	0	0	0
Total costs	**4 287 826**	**309 585**	**3 978 241**
Life years gained (F0)	1.89	0.07	1.83
Life years gained (F1)	2.24	0.08	2.16
Life years gained (F2)	5.31	2.78	2.53
Life years gained (F3)	2.20	2.55	-0.35
Life years gained (F4)	2.08	2.97	-0.89
Life years gained (DCC)	0.52	0.92	-0.40
Life years gained (HCC)	0.27	0.40	-0.13
Life years gained (LT)	0.01	0.01	0.00
Life years gained (PLT)	0.11	0.18	-0.07
Total life years	**14.62**	**9.95**	**4.67**
QALYs (F0)	1.73	0.06	1.67
QALYs (F1)	1.97	0.07	1.90
QALYs (F2)	4.60	2.36	2.23
QALYs (F3)	1.94	2.22	-0.28
QALYs (F4)	1.75	2.47	-0.72
QALYs (DCC)	0.38	0.67	-0.29
QALYs (HCC)	0.22	0.32	-0.10
QALYs (LT)	0.00	0.01	0.00
QALYs (PLT)	0.09	0.14	-0.06
QALYs (adverse reactions)	-0.00	-0.00	-0.00
Total QALYs	**12.68**	**8.31**	**4.36**

Incremental costs per life year gained	**852 495**
Incremental cost per QALY gained (ICER)	**912 105**

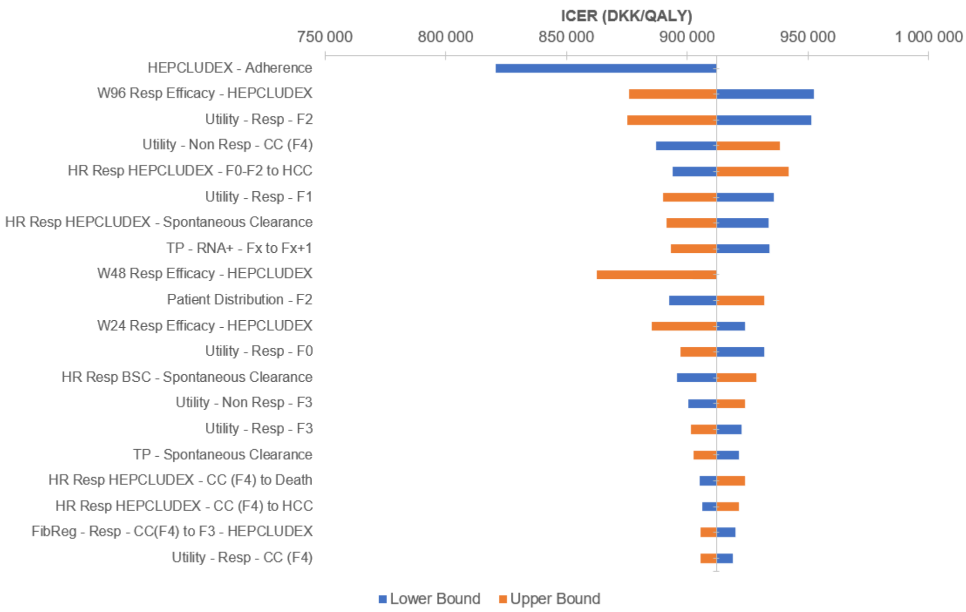
Abbreviations: BSC = best supportive care; DCC = decompensated cirrhosis; F0-4 = fibrosis stage 0-4; HCC = hepatocellular carcinoma; ICER = inctremental cost-effectiveness ratio; LT = liver transplant; PLT = post-liver transplant; QALY = quality-adjusted life year

12.2 Sensitivity analyses

12.2.1 Deterministic sensitivity analyses

The 20 parameters with the greatest influence on the results are shown in Figure 20. Most influential is Hepcludex adherence. Second most is the response of the composite endpoint at week 96 among patients on Hepcludex treatment. The third most influential parameter is the modelled health state utility in F2 for responders.

Figure 28 Deterministic sensitivity analyses



Abbreviations: DKK = Danish krona; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year

Table 48 displays the one-way sensitivity analyses performed. The ICER remained relatively stable under all tested assumptions. As the benefits continue to accrue over time setting the discount rate to 0% decreases the ICER substantially. This is also reflected in the sensitivity analysis of a shorter time horizon in which the ICER increased, which is in line with the chronic nature of the disease which requires a lifetime horizon for capturing all the effects and costs. As stated, treatment should continue as long as there is a clinical benefit, this rule was tested with different assumptions of the stopping rules implementations. Treating patients beyond where the treatment provides a clinical benefit result in a higher ICER and highlights the importance of properly implemented stopping rules for efficient use of the healthcare budget.

Table 66 One-way sensitivity analyses results

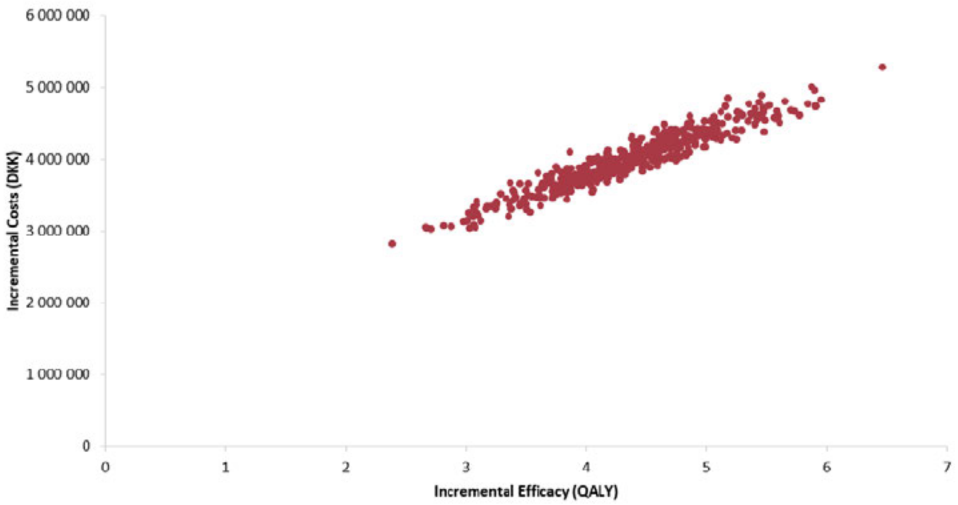
	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case	N/A	N/A	3 978 241	4.36	912 105
Discount rates, costs and effects	0%	Influential parameter	6 620 884	10.51	629 771
	5%		3 401 566	3.19	1 067 543
Time horizon	20 years	Influential parameter	3 092 661	2.01	1 538 202
	40 years		3 833 718	3.91	980 788
Treatment population	F2 removed	Different assumption of eligible population	3 544 259	4.75	745 965
Adverse events	Excluded	Test of sensitivity	3 978 327	4.36	912 254
Responder disease progression HR source	All sourced from Gish et al. (87) instead of Fx to Fx+1 and F4 to DCC being calculated	Test of sensitivity	3 958 577	4.25	930 554
Treatment discontinuation of patients who have not achieved a combined response at w. 96	Excluded	Test of sensitivity	5 471 647	4.49	1 218 680
Treatment discontinuation of patients who have achieved 96 weeks of HDV RNA undetectability at week 144, 192 and 240	Excluded	Test of sensitivity	5 758 048	4.36	1 320 054
Fibrosis health state utility source	Scalone et al. 2012 instead of MYR301	Test of sensitivity	3 978 241	4.51	881 457

Abbreviations: DKK = Danish krona; Fx = fibrosis stage x; HBV = hepatitis B virus; ICER = incremental cost-effectiveness ratio; N/A = not applicable; QALY = quality-adjusted life year

12.2.2 Probabilistic sensitivity analyses

The ICER in the probabilistic sensitivity analysis amounted to 914 200 DKK per QALY gained, similar to the base case ICER of 912 105 DKK per QALY gained. In the probabilistic simulation the QALY gain was marginally lower of 4.34 compared to the deterministic simulation's QALY gain of 4.36 over a lifetime horizon. Average costs were on the contrary lower and thus offsetting the slightly lower QALY gain resulting in the very similar ICER.

Figure 29 Probabilistic sensitivity analysis



Abbreviations: DKK = Danish krona; QALY = quality-adjusted life year

13. Budget impact analysis

The number of new patients expected to be treated with bulevirtide over the next five-year with and without recommendation from DMC are presented in Table 49. With respect to expected patient numbers in the scenario without a positive recommendation, the expectation is that [redacted] patients will remain on treatment, as it is the case today. The budget impact of recommendation during the first 5 years is presented in Table 50. The estimated budget impact in year 5 is 10 million DKK at list price.

Number of patients (including assumptions of market share)

Table 67 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		
Hepcludex	21	32	43	44	45
BSC	20	10	0	0	0
			Non-recommendation		

Hepcludex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC = best supportive care

Budget impact

Table 68 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	13.4	19.3	18.9	14.9	11.2
The medicine under consideration is NOT recommended	1.7	1.7	1.3	1.3	1.2
Budget impact of the recommendation	11.7	17.5	17.6	13.6	10.0

14. List of experts

Name	Job function	Workplace
[redacted]	[redacted]	[redacted]

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Appendix A. Main characteristics of studies included

Table 69 Main characteristics of studies included

Trial name: A Multicenter, Open-label, Randomized Phase 3 Clinical Study to Assess Efficacy and Safety of Bulevirtide in Patients with Chronic Hepatitis Delta - MYR301	NCT number: NCT03852719
Objective	The overall objective of this study was to evaluate the efficacy of bulevirtide administered subcutaneously at a dose of 2 mg or 10 mg once daily for treatment of CHD in comparison to delayed treatment (BSC).
Publications – title, author, journal, year	Wedemeyer H, Aleman S, Brunetto MR, Blank A, Andreone P, Bogomolov P, Chulanov V, Mamonova N, Geyvandova N, Morozov V, Sagalova O, Stepanova T, Berger A, Manuilov D, Suri V, An Q, Da B, Flaherty J, Osinusi A, Liu Y, Merle U, Schulze Zur Wiesch J, Zeuzem S, Ciesek S, Cornberg M, Lampertico P; MYR301 Study Group. A Phase 3, Randomized Trial of Bulevirtide in Chronic Hepatitis D. N Engl J Med. 2023 Jul 6;389(1):22-32. doi: 10.1056/NEJMoa2213429. Epub 2023 Jun 22. Wedemeyer H, Aleman S, Brunetto M, Blank A, Andreone P, Bogomolov P, et al. (2024). Bulevirtide monotherapy in patients with chronic HDV: Efficacy and Safety Results Through Week 96 from a Phase III Randomized Trial. J Hepatol. 2024; 81(4): 621-629.
Study type and design	This was a multicenter, open-label, randomized trial. Eligible patients were assigned in a 1:1:1 ratio, with stratification according to the presence or absence of cirrhosis.
Sample size (n)	150 patients, 49 patients in the bulevirtide 2 mg arm and 51 patients in the BSC arm
Main inclusion criteria	1. Provision of signed and dated informed consent form. 2. Positive serum anti-hepatitis delta virus (HDV) antibody results or polymerase chain reaction (PCR) results for serum/ plasma HDV ribonucleic acid (RNA) for at least 6 months before screening. 3. Positive PCR results for serum/plasma HDV RNA at screening. 4. Alanine transaminase level > 1 x upper limit of normal (ULN), but less than 10 x ULN. 5. Serum albumin > 28 g/L. 6. Negative urine pregnancy test for females of childbearing potential.

	7. Inclusion criteria for females: • Postmenopausal for at least 2 years, or • Surgically sterile (total hysterectomy or bilateral oophorectomy, bilateral tubal ligation, staples, or another type of sterilization), or • Abstinence from heterosexual intercourse throughout the study, or • Willingness to use highly effective contraception (double barrier method or barrier contraception in combination with hormonal or intrauterine contraceptive) throughout the study and for 3 months after the last dose of the study medication for individuals discontinued during the treatment period. 8. Individuals must agree to use a highly effective contraception (double barrier method or barrier contraception in combination with hormonal or intrauterine contraceptive used by female partners) and not to donate sperm throughout the study and for 3 months after the last dose of the study medication for individuals discontinued during the treatment period.
Main exclusion criteria	1. Child-Pugh hepatic insufficiency score over 7 points. Uncomplicated oesophageal varices allowed; Individuals with current bleeding or ligation, or history of bleeding or ligation within the last 2 years are excluded. 2. Hepatitis C virus (HCV) or uncontrolled human immunodeficiency virus (HIV) coinfection. Individuals with HCV antibodies can be enrolled, if screening HCV RNA test is negative. Individuals with HIV infection can be enrolled if cluster of differentiation (CD4+) cell counts are >500/mL and HIV RNA is below limit of detection for at least 12 months. 3. Creatinine clearance < 60 mL/min as estimated using Cockcroft-Gault formula. 4. Total bilirubin ≥ 34.2 µmol/L. (Individuals with higher total bilirubin values may be included after the consultation with the Study Medical Monitor, if such elevation can be clearly attributed to Gilbert's syndrome associated with low-grade hyperbilirubinemia.) 5. Evidence of an active or suspected malignancy or a history of malignancy, or an untreated pre-malignancy disorder within the last 5 years (with the exception of successfully treated carcinoma of the cervix in situ and successfully treated basal cell carcinoma and squamous cell carcinoma not less than 1 year prior to screening [and no more than 3 excised skin cancer

within the last 5 years prior to screening]) or history of hepatic carcinoma.

6. Systemic connective tissue disorders.
7. New York Heart Association (NYHA) class III-IV congestive heart failure.
8. Individuals with uncontrolled arterial hypertension: systolic blood pressure > 150 mm Hg and/ or diastolic blood pressure > 100 mm Hg at Screening.
9. Previous or unstable concurrent diseases or conditions that prevent individual's enrolment into the study.
10. Individuals with mental disorders or social circumstances that preclude them from following protocol requirements.
11. Current or previous (within last 2 years) decompensated liver disease, including coagulopathy, hepatic encephalopathy and oesophageal varices haemorrhage.
12. One or more additional known primary or secondary causes of liver disease, other than hepatitis B (e.g., alcoholism, autoimmune hepatitis, malignancy with hepatic involvement, hemochromatosis, alpha-1 antitrypsin deficiency, Wilson's Disease, other congenital or metabolic conditions affecting the liver, congestive heart failure or other severe cardiopulmonary disease, etc.). Gilbert's syndrome, a benign disorder associated with low-grade hyperbilirubinemia, will not exclude individuals from participation in this trial. Autoimmune hepatitis stigmata attributed to HDV infection in the opinion of the investigator are allowed.
13. White blood cells (WBC) count < 3000 cells/mm^3 (<1500 if African individuals).
14. Neutrophil count < 1500 cells/mm^3 (<1000 if African individuals).
15. Platelet count < 60,000 cells/mm^3.
16. Use of prohibited psychotropic agents at Screening.
17. Use of interferons within 6 months before Screening.
18. History of solid organ transplantation.
19. Current alcohol abuse or alcohol abuse within 6 months prior to enrolment in this study; past or current drug addict.
20. History of disease requiring regular use of systemic glucocorticosteroids (inhalative glucocorticosteroids are allowed) or other immunosuppressants.
21. Pregnant or breast-feeding females.

	22. Participation in another clinical study with investigational drugs within 30 days prior to randomization. 23. Receipt of bulevirtide previously, e.g. in clinical trials. 24. Inability to follow protocol requirements and undergo all protocol procedures. NOTE: Individuals with medical contraindication for liver biopsy are allowed to participate in this study. Such individuals will exempt from liver biopsy requirements in this study.
Intervention	Patients received 1 dose of either bulevirtide 2 mg (n=49) or 10 mg (n=50) once daily (every 24 hours ± 4 hours) by subcutaneous injection as monotherapy or in co-administration with a NA for treatment of underlying HBV infection.
Comparator(s)	After an observational period of 48 weeks (BSC), patients in the delayed treatment arm received bulevirtide 10 mg (n=51) once daily (every 24 hours ± 4 hours) by subcutaneous injection for 96 weeks and were followed for up to 96 weeks.
Follow-up time	After EOT (Week 144), patients entered a 96-weeks follow-up period. In total, 57.3% of patients completed the study at Week 240.
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	The primary efficacy endpoint was the proportion of participants achieving combined response at Week 48, defined as the fulfilment of undetectable (< lower limit of quantitation [LLOQ], target not detected) HDV RNA or decreased by ≥ 2 log10 IU/mL from baseline and alanine aminotransferase (ALT) normalisation. Secondary endpoints are listed below: • The proportion of participants with undetectable HDV RNA at Week 48 • The proportion of participants with ALT normalisation at Week 48 • The proportion of participants with undetectable HDV RNA 24 weeks after scheduled end of treatment (sustained virologic response at follow-up Week 24) • The proportion of participants with undetectable HDV RNA 48 weeks after scheduled end of treatment (sustained virologic response at follow-up Week 48) • Change from baseline in liver stiffness as measured by elastography at Weeks 48, 96, 144, 192, and 240 • The proportion of participants with HDV RNA decrease by ≥ 2 log10 IU/mL or undetectable HDV RNA at Week 48

Exploratory endpoints are listed below:

- The proportion of participants with a change from baseline in necroinflammation as assessed at liver biopsies (for available appropriate biopsy specimens)
- The proportion of participants with a change from baseline in fibrosis as assessed at liver biopsies (for available appropriate biopsy specimens)
- The proportion of participants with combined response at all postbaseline assessments of HDV RNA and ALT
- The proportion of participants with HDV RNA decrease by ≥ 2 log10 IU/mL from baseline at all postbaseline assessments
- The proportion of participants with undetectable HDV RNA at all postbaseline assessments
- Change from baseline in HDV RNA at all postbaseline assessments
- The proportion of participants with ALT normalisation at all postbaseline assessments
- Change from baseline in ALT at all postbaseline assessments
- Change from baseline in serum alpha-2-macroglobulin (fibrosis marker) at all postbaseline assessments
- The proportion of participants with hepatitis B surface antigen (HBsAg) response (HBsAg decrease by ≥ 1 log10 IU/mL) at all postbaseline assessments
- The proportion of participants with HBsAg loss without seroconversion at all postbaseline assessments
- The proportion of participants with HBsAg loss with seroconversion (presence of anti-HBsAg) at all postbaseline assessments
- Change from baseline in HBsAg at all postbaseline assessments
- Change from baseline in HBV DNA at all postbaseline assessments
- Incidence of liver-related clinical events at all postbaseline assessments
- Number of liver-related hospitalizations and duration of each hospitalization at all postbaseline assessments
- Appearance and concentration of anti-BLV antibodies

	• Resistance testing (HBV sequencing genotypic assay [sequencing analysis] with focus on the HBV envelope, phenotypic resistance assay, and HDV sequencing genotypic assay [sequencing analysis]) • Other parameters in liver biopsy samples • Hepatitis B e antigen (HBeAg) and hepatitis B e antibody (HBeAb) status at all postbaseline assessments (for participants with positive HBeAg at screening)
Method of analysis	All analyses were either performed on the Full Analysis Set (FAS), the Per Protocol (PP) Analysis Set or the Safety Population. The primary endpoint was based on the FAS. Two 2-sided Fisher tests at an overall significance level of 0.05 were performed. Participants with missing assessment at 48 weeks in the primary endpoint were handled as non-responders unless it is related to COVID-19 in which case missing values were imputed using the last observation carried forward (LOCF) approach. In terms of a hierarchical testing procedure the second null hypothesis was not rejected if the first null hypothesis could not be rejected. Confidence intervals (CIs) with confidence probability adjusted to the respective significance levels using exact unconditional confidence limits based on the score statistic were presented for the rate differences. Clopper-Pearson 95% CIs were calculated for the single rates. To determine the proportion of participants with undetectable HDV RNA at Week 48, a 2-sided Fisher test was performed. CIs with confidence probability adjusted to the respective significance levels using exact unconditional confidence limits based on the score statistic were presented for the rate differences. Clopper-Pearson 95%-CIs were calculated for the single rates. Participants with missing assessment at 48 weeks in undetectable HDV RNA were handled in the same way as the primary endpoint described above. All other efficacy data was analysed descriptively. Rates of participants with ALT normalisation at Week 48 and undetectable HDV RNA 24 and 48 weeks after scheduled end of treatment were analysed analogously to the primary endpoint in the framework of explorative analysis without adjusting for multiple testing. Participants with missing assessment at 48 weeks in the other secondary endpoints or exploratory endpoints were handled as non-responder, regardless the reason for the absence. Change from baseline in liver stiffness as measured by elastography was analysed in a mixed-effects model for repeated measures model with fixed-effect factors treatment, region, presence of cirrhosis, visit and treatment-by-visit interaction and the baseline values as covariable. CIs were based on estimated means (least square means) and corresponding t-statistics. Restricted maximum likelihood was

	employed to fit the model for primary analysis. Within participant variation was modelled as random effect with unstructured covariance structure. The Kenward-Roger approximation was used to estimate the denominator degrees of freedom. If the model still failed to converge, the model was fit using covariance matrices of the following order specified by a decreasing number of covariance parameters until convergence was met: heterogeneous Toeplitz, heterogeneous autoregressive, Toeplitz, and autoregressive.
Subgroup analyses	Subgroup analyses were pre-specified and included 1) Subjects with or without cirrhosis, 2) anti-drug-antibodies (ADA) positive or negative subjects, 3) subjects who were HBeAg positive or negative at screening and 4) subject who did or did not receive concomitant HBV medication (NA). Analyses were performed as described in ''Method of analyses'', depending on the investigated endpoint.
Other relevant information	None.

Abbreviations: ADA = anti-drug-antibody; ALT = alanine aminotransferase; BSC = best supportive care; CI = confidence interval; HBeAb = hepatitis B e antibody; FAS = Full Analysis Set; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HDV = hepatitis delta virus; HIV = human immunodeficiency virus; LLOQ = lower limit of quantitation; LOCF = last observation carried forward; NA = nucleoside/nucleotide analogue; NYHA = New York Heart Association; PCR = polymerase chain reaction; PP = Per Protocol; RNA = ribonucelic acid; ULN = upper limit of normal; WBC = white blood cell

Source: (35, 54, 55)

Appendix B. Efficacy results per study

Results per study

Table 70 Results per study

Results of MYR301 (NCT03852719)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Combined response at Week 48, n (%; 95% CI)	Bulevirtide 2 mg	49	22 (44.9; 30.7, 59.8)	21 (42.9%)	96% CI 27.0% to 58.5%	< 0.0001	NR	NR	NR	Two 2-sided Fisher tests at an overall significance level of 0.05 were performed. CIs with confidence probability adjusted to the respective significance levels using exact unconditional confidence limits based on the score statistic were presented for the rate differences.	Gilead Sciences Inc. (35), Gilead Sciences Inc. (54), Wedemeyer et al. (69)
	BSC	51	1 (2; 0, 10.4)								
Undetectable HDV RNA at Week 48, n (%; 95% CI)	Bulevirtide 2 mg	49	6 (12.2; 4.6, 24.8)	6 (12.2%)	NR	NR	NR	2.89, 21.51[a]	0.0102[a]	A 2-sided Fisher test was performed. CIs with confidence probability adjusted to the respective significance levels using exact unconditional confidence limits based on the	Gilead Sciences Inc. (35), Gilead Sciences Inc. (54), (69)
	BSC	51	0 (0; 0, 7)								

										score statistic were presented for the rate differences.	
Undetectable HDV RNA at Week 48 after scheduled EOT, n (%; 95% CI)	Bulevirtide 2 mg	49	8 (16.3; 7.3, 29.7)	NA	NA	NA	NA	NA	NA	Comparison based on Fisher's exact test. Exact unconditional confidence intervals based on scores for the proportion differences are presented, with corresponding confidence levels of 95%.	Gilead Sciences Inc. (35), Gilead Sciences Inc. (54)
	BSC	51	NA								
Alanine aminotransferase normalisation at Week 48, n (%; 95% CI)	Bulevirtide 2 mg	49	25 (51;36.3, 65.6)	19 (39.3%)	20, 55.8	< 0.0001	NR	NR	NR	Comparison based on Fisher's exact test. Exact unconditional confidence intervals based on scores for the proportion differences are presented, with corresponding confidence levels of 95%.	Gilead Sciences Inc. (35), Gilead Sciences Inc. (54), (69)
	BSC	51	6 (11.8%; 4.4, 23.9)								
Change from baseline in liver stiffness at Weeks 48, 96, 144, 192, and 240, kPa	Bulevirtide 2 mg	49	Week 48: -3.06 (-4.67, -1.45) Week 96: -4.31 (−5.54, −3.08) Week 144: -5.24 (−6.85, −3.63)	-3.93	-6.23, -1.63	0.0009	NR	NR	NR	Analysed in a mixed-effects model for repeated measures model with fixed-effect factors. CIs were based on least square means and corresponding t-statistics.	Gilead Sciences Inc. (35), Gilead Sciences Inc. (54)

			Week 192: -3.74 (−5.28, −2.20) Week 240: -1.2 (−3.71, 1.31)								
	BSC	51	Week 48: 0.87 (-0.79, 2.53)								
Virologic response, n (%; 95% CI)	Bulevirtide 2 mg	49	36 (73.5; 58.9, 85.1)	34 (69.5%)	54.1, 81.9	< 0.0001	NR	NR	NR	A 2-sided Fisher test was performed. CIs with confidence probability adjusted to the respective significance levels using exact unconditional confidence limits based on the score statistic were presented for the rate differences.	Gilead Sciences Inc. (35), Gilead Sciences Inc. (54), (69)
	BSC	51	2 (4; 0.5, 13.5)								
Change From baseline in HBsAg levels at Week 48, Week 144 and Week 240, log10 IU/mL (SD)	Bulevirtide 2 mg	49	Week 48: 0.09 (0.202) Week 144: -0.36 (0.596) Week 240: -0.54 (0.962)	NR	NR	NR	NR	NR	NR	N/A	Gilead Sciences Inc. (35), Gilead Sciences Inc. (54)
	BSC	51	Week 48: 0.01 (0.38)								

Change in fibrosis from baseline to Week 48 (METAVIR fibrosis stage), n (%)	Bulevirtide 2 mg	24	Improving: 12 (50) No change: 7 (29.2) Worsening: 5 (20.8)	NR	NR	NR	NR	NR	NR	N/A	Gilead Sciences Inc. (35), Gilead Sciences Inc. (54)
	BSC	27	Improving: 8 (29.6) No change: 9 (33.3%) Worsening: 10 (37)								

Abbreviations: BSC = best supportive care; CI = confidence interval; EOT = end of treatment; HBsAg = hepatitis B surface antigen; HDV = hepatitis delta virus; kPa = kilopascal; N/A = not applicable; NR = not reported; SD = standard deviation

[a] The comparison between the bulevirtide 2 mg arm and the BSC arm was not included in formal testing.

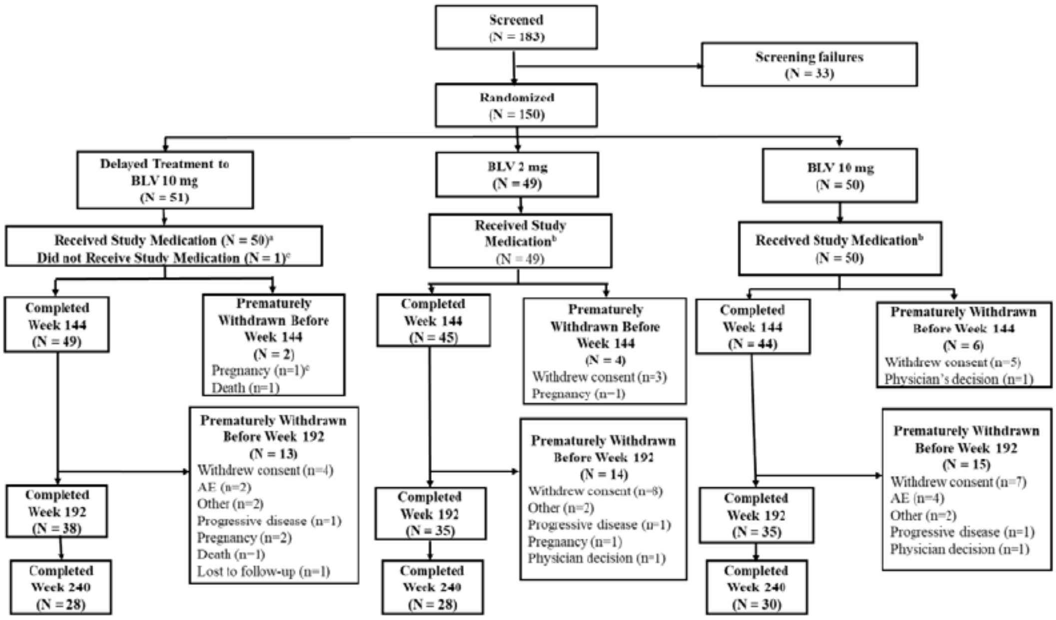
Sources: (35, 54, 69)

B.1 Outcomes in MYR301 – detailed description

B.1.1 Patient disposition and patient characteristics

The patient disposition is depicted in Figure 22 (35).

Figure 30 Disposition of Participants to Week 240 (All Screened Participants)



Abbreviations: AE = adverse event; BLV = bulevirtide; DT = delayed treatment

[a] At Week 48 (BSC).

[b] At Week 0.

[c] One participant in the DT group was discontinued before Week 48 due to pregnancy.

Source: (35)

Table 53 presents a summary of participant demographics and other baseline characteristics assessed at baseline. The median age was 41.0 years (range: 19 to 62 years). Overall, the majority of participants were White (82.7%), and over half of the participants were male (57.3%). The overall median (Q1, Q3) value for BMI at baseline was 24.76 (22.40, 27.04) kg/m² (35).

Table 71 Demographic and baseline characteristics (Full Analysis Set)

	BSC[a] (N=51)	Bulevirtide 2 mg (N=49)
Age		
N	51	49
Mean (SD)	41 (7.5)	44 (9.0)
Median	40	43
Q1, Q3	35, 45	39, 49
Min, max	27, 61	19, 62
Sex at birth, n (%)		

Male	26 (51.0%)	30 (61.2%)
Female	25 (49.0%)	19 (38.8%)
Race, n (%)		
Asian	11 (21.6%)	8 (16.3%)
Black or African American	0	0
White	40 (78.4%)	41 (83.7%)
Body mass index (kg/m^2)		
N	51	49
Mean (SD)	25.26 (3.863)	24.40 (3.086)
Median	25.14	24.22
Q1, Q3	22.36, 27.90	22.37, 26.67
Min, max	18.48, 34.78	19.47, 31.35
Body mass index category, n (%)		
< 30 kg/m^2	46 (90.2%)	48 (98.0%)
≥ 30 kg/m^2	5 (9.8%)	1 (2.0%)

Abbreviations: BSC = best supportive care; Q1/Q3 = first/third quartile; SD = standard deviation

[a] From Week 48 through the end of treatment, participants received bulevirtide 10 mg.

Baseline value was the last available value collected on or prior to the first dose of bulevirtide and the last available value collected prior to or at randomization for the BSC arm.

Source: (35)

Table 54 presents a summary of the baseline disease characteristics. Baseline disease characteristics were generally similar among the study arms. Overall, almost half of the participants (46.9%) in the bulevirtide 2 mg arm had cirrhosis at the time of original baseline (at randomization), and all these participants were Child-Pugh Class A; 69.6% and 79.2% in the bulevirtide arm and BSC arm, respectively, had a score of 5 and 30.4% and 20.8% had a score of 6, respectively. The mean (standard deviation [SD]) HDV RNA in the bulevirtide arm was 5.1 (1.194) log10 IU/mL and 5.08 (1.358) log10 IU/mL in the BSC arm, and the mean (SD) ALT at baseline in the bulevirtide arm was 108 (62.5) U/L and 102 (61.9) U/L in the BSC arm. All patients had HDV genotype HDV-1. At baseline, 91.8% of participants in the bulevirtide arm were HBeAg negative, compared to 92.2% of participants in the BSC arm. At baseline, HBsAg levels were 3.67 (0.515) log10 IU/mL in the bulevirtide arm and 3.68 (0.465) log10 IU/mL in the BSC arm, respectively. A total of 32 participants (65.3%) in the bulevirtide arm received concomitant oral anti-HBV treatment, 82 participants (54.7%) of whom had started anti-HBV treatment prior to baseline compared to 33 participants (64.7%) in the BSC arm (35).

Table 72 Baseline Disease Characteristics (Full Analysis Set)

	BSC[a] (N=51)	Bulevirtide 2 mg (N=49)
Cirrhosis status at randomization		
Presence	24 (47.1%)	23 (46.9%)
Absence	27 (52.9%)	26 (53.1%)
Baseline Child-Pugh score (category)[b]		
5	19 (79.2%)	16 (69.6%)
6	5 (20.8%)	7 (30.4%)
Baseline Child-Pugh class[b]		
A	24 (100.0%)	23 (100.0%)
HDV genotype		
Genotype HDV-1	51 (100.0%)	49 (100.0%)
HBV genotype[c]		
Genotype A	2 (3.9%)	2 (4%)
Genotype D	44 (86.3%)	47 (95.9%)
Genotype E	0	0
No data	3 (5.9%)	0
Unclassified	2 (3.9%)	0
Baseline HBV DNA (log10 IU/mL)		
N	51	49
Mean (SD)	0.89 (0.989)	1.31 (1.280)
Baseline HBV DNA category		
< LLOQ target not detected	12 (23.5%)	6 (12.2%)
< LLOQ target detected	12 (23.5%)	10 (20.4%)
≥ LLOQ	27 (52.9%)	33 (67.3%)
Baseline HDV RNA (log10 IU/mL)		
N	51	49

Mean (SD)	5.08 (1.358)	5.10 (1.194)
HBeAg status		
Positive	4 (7.8%)	4 (8.2%)
Negative	47 (92.2%)	45 (91.8%)
Baseline HBsAg (log10 IU/mL)		
N	51	47
Mean (SD)	3.68 (0.465)	3.67 (0.515)
Baseline ALT (U/L)		
Mean (SD)	102 (61.9)	108 (62.5)
Baseline total bile salts (µmol/L)		
N	51	48
Mean (SD)	15.8 (11.94)	16.6 (14.06)
Baseline creatinine clearance category		
≥ 60 to < 90 mL/min	10 (19.6%)	9 (18.4%)
≥ 90 mL/min	41 (80.4%)	40 (81.6%)
Baseline liver stiffness (kPa)		
Mean (SD)	15.3 (8.95)	14.0 (8.19)
Baseline liver stiffness category		
< 12 kPa	26 (51.0%)	24 (49.0%)
12-20 kPa	15 (29.4%)	16 (32.7%)
> 20 kPa	10 (19.6%)	9 (18.4%)
Concomitant oral anti-HBV medication		
No	18 (35.3%)	17 (34.7%)
Yes	33 (64.7%)	32 (65%)

Abbreviations: BSC = best supportive care; ALT = alanine aminotransferase; DT = delayed treatment; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HDV = hepatitis delta virus; kPa = kilopascals; LLOQ = lower limit of quantitation

[a] From Week 48 through the end of treatment, participants received BLV 10 mg.

[b] Child-Pugh score and class are presented for participants with cirrhosis only, with percentages based on the number of participants with cirrhosis with available Child-Pugh scores at baseline.

[c] HBV genotyping was performed at the first occasion of positive HBV DNA result, which could be postbaseline.

Baseline value was the last available value collected on or prior to the first dose of bulevirtide for the BLV 2 mg group, and the last available value collected prior to or at randomization for the BSC group.

Anti-HBV medications were defined as oral medications with preferred names containing terms of tenofovir, tenofovir alafenamide, tenofovir disoproxil fumarate, tenofovir disoproxil, entecavir, adefovir, lamivudine, telbivudine, and adefovir dipivoxil.

Source: (35, 69, 70)

B.1.2 Combined response

The primary efficacy endpoint was the combined response (undetectable HDV RNA or HDV RNA decreased ≥ 2 log10 IU/mL from baseline combined with ALT normalisation) at Week 48. As shown in Table 55, the proportion of participants (95% CI) who achieved combined response at Week 48 for each of the arms was as follows (35):

- BSC arm: 2.0% (95% CI: 0.0%-10.4%)
- Bulevirtide 2 mg arm: 44.9% (95% CI: 30.7%-59.8%)

Differences in proportions (96% CI) of responders at Week 48 for the combined response between each of the immediate BLV groups and the DT group were both statistically significant (p < 0.04). The difference in proportions (96% CI) and the p-value comparing the 2 groups are presented below:

- Bulevirtide 2 mg arm versus BSC arm: 42.9% (96% CI: 27.0%-58.5%; p < 0.0001)

Additionally, the combined response at each study visit is depicted up to follow-up Week 96 (Week 240), starting from Week 72. For the BSC arm, data is only available until Week 48 (Table 55) (35).

Table 73 Combined Response by visit up to Week 240 (Full Analysis Set), Missing = Failure

	BSC[a] (N=51)	Bulevirtide 2 mg (N=49)
Week 24		
Responder, n (%)	0	17 (34.7%)
95% CI	0.0% to 7.0%	21.7% to 49.6%
Response rate diff vs BSC	-	36.7%
99% CI	-	20.0% to 56.1%
p-value	-	< 0.0001
Week 48		
Responder, n (%)	1 (2.0%)	22 (44.9%)
95% CI	0.0% to 10.4%	30.7% to 59.8%
Response rate diff vs BSC	-	42.9%
96% CI	-	27.0% to 58.5%
p-value	-	< 0.0001
Week 72		

Responder, n (%)	-	22 (44.9%)
95% CI	-	30.7% to 59.8%
Week 96		
Responder, n (%)	-	27 (55.1%)
95% CI	-	40.2% to 69.3%
Week 144		
Responder, n (%)	-	28 (57.1%)
95% CI	-	42.2% to 71.2%
Week 168 (follow-up Week 24)		
Responder, n (%)	-	11 (22.4%)
95% CI	-	11.8% to 36.6%
Week 192 (follow-up Week 48)		
Responder, n (%)	-	11 (22.4%)
95% CI	-	11.8% to 36.6%
Week 240 (follow-up Week 96)		
Responder, n (%)	-	12 (24.5%)
95% CI	-	13.3% to 38.9%

Abbreviations: BSC = best supportive care; CI = confidence interval; diff = difference

Combined response: undetectable HDV RNA (< LLOQ, target not detected) or HDV RNA decreased ≥ 2 log10 IU/mL from baseline combined with ALT normalisation.

[a] From Week 48 through the end of treatment, participants received bulevirtide 10 mg.

Baseline value was the last available value collected on or prior to the first dose of bulevirtide for the BLV 2 mg group, and the last available value collected prior to or at randomization for the BSC group.

The 95% CI for each group was based on the Clopper-Pearson exact method. The 99% and 96% exact unconditional CI based on the score statistic was presented for response rate difference at Week 24 and Week 48 respectively.

Source: (35, 70)

B.1.3 Undetectable HDV RNA

As shown in Table 56, the proportion of participants who achieved undetectable HDV RNA increased from Week 24 to Week 144 in the bulevirtide 2 mg arm. At Week 48, the proportion of responders for undetectable HDV RNA was as follows (35):

- BSC arm: 0.0% (95% CI: 0.0%-7.0%)
- Bulevirtide 2 mg arm: 12.2% (95% CI: 4.6%-24.8%)

Table 74 Undetectable HDV RNA by Visit up to Week 240 (Full Analysis Set), Missing = Failure

	BSC[a] (N=51)	Bulevirtide 2 mg (N=49)
Week 24		
Responder, n (%)	0 (0%)	3 (6.1%)
95% CI	0.0% to 7.0%	1.3% to 16.9%
Week 48		
Responder, n (%)	0 (0%)	6 (12.2%)
95% CI	0.0% to 7.0%	4.6% to 24.8%
Response rate diff vs BSC	-	12.2%
95% CI	-	2.89, 21.51[b]
p-value	-	0.0102[b]
Week 72		
Responder, n (%)	-	11 (22.4%)
95% CI	-	11.8% to 36.6%
Week 96		
Responder, n (%)	-	10 (20.4%)
95% CI	-	10.2% to 34.3%
Week 144		
Responder, n (%)	-	14 (28.6%)
95% CI	-	16.6% to 43.3%
Week 168 (follow-up Week 24)		
Responder, n (%)	-	9 (18.4%)
95% CI	-	8.8% to 32.0%

Week 192 (follow-up Week 48)		
Responder, n (%)	-	8 (16.3%)
95% CI	-	7.3% to 29.7%
Week 240 (follow-up Week 96)		
Responder, n (%)	-	10 (20.4%)
95% CI	-	10.2% to 34.3%

Abbreviations: BSC = best supportive care; CI = confidence interval; diff = difference

[a] From Week 48 through the end of treatment, participants received bulevirtide 10 mg.

[b] The comparison between the bulevirtide 2 mg arm and the BSC arm was not included in formal testing.

The 95% CI for each group was based on the Clopper-Pearson exact method. The 99% and 96% exact unconditional CI based on the score statistic was presented for response rate difference at Week 24 and Week 48 respectively.

Source: (35, 70)

B.1.3.1 HDV RNA levels (log10 IU/mL) and change from baseline over time

Mean HDV RNA levels progressively declined over the 144-week treatment for the bulevirtide 2 mg arm. HDV RNA (log10 IU/mL) levels at the posttreatment follow-up visits were increased when compared with those seen at the EOT once the participants were taken off bulevirtide treatment. Descriptive statistics for the HDV RNA (log10 IU/mL) values and changes from baseline at Weeks 24, 48, 96, 144, 168 (follow-up Week 24), 192 (follow-up Week 48), and 240 (follow-up Week 96) are presented in Table 57 (35).

Table 75 Change from baseline in HDV RNA (log10 IU/mL) over time (Full Analysis Set), observed cases

	BSC[a] (N=51)	Bulevirtide 2 mg (N=49)
Baseline		
N	51	49
Mean (SD)	5.08 (1.358)	5.10 (1.194)
Median	5.38	5.23
Q1, Q3	4.28, 6.12	4.61, 5.77
Min, max	1.40, 7.46	2.04, 7.06
Change from baseline at Week 24		
N	49	48
Mean (SD)	−0.12 (0.763)	−2.26 (1.248)
Median	−0.08	−2.18
Q1, Q3	−0.28, 0.23	−3.04, −1.49

Min, max	−3.73, 1.41	−5.23, 0.02
Change from baseline at Week 48		
N	50	48
Mean (SD)	−0.05 (1.047)	−2.62 (1.415)
Median	0.09	−2.64
Q1, Q3	−0.70, 0.57	−3.30, −1.92
Min, max	−3.77, 2.24	−5.60, 0.35
Change from baseline at Week 96		
N	-	47
Mean (SD)	-	−3.17 (1.543)
Median	-	−3.33
Q1, Q3	-	−4.17, −2.39
Min, max	-	−7.00, 0.36
Change from baseline at Week 144		
N	-	45
Mean (SD)	-	−3.20 (1.625)
Median	-	−3.26
Q1, Q3	-	−4.36, −2.16
Min, max	-	−7.00, 0.17
Change from baseline at Week 168 (follow-up Week 24)		
N	-	38
Mean (SD)	-	−2.13 (2.013)
Median	-	−2.00
Q1, Q3	-	−3.86, −0.15
Min, max	-	−5.84, 1.22
Change from baseline at Week 192 (follow-up Week 48)		
N	-	35
Mean (SD)	-	−1.65 (2.176)
Median	-	−1.56

Q1, Q3	-	−3.61, 0.22
Min, max	-	−5.60, 1.62
Change from baseline at Week 240 (follow-up Week 96)		
N	-	28
Mean (SD)	-	−2.44 (2.223)
Median	-	−2.72
Q1, Q3	-	−4.03, −0.47
Min, max	-	−7.00, 1.86

Abbreviations: BSC = best supportive care; HDV = hepatitis delta virus; Q1/Q3 = first/third quartile; SD = standard deviation

[a] From Week 48 through the end of treatment, participants received BLV 10 mg. The actual dose of BLV administered was 1.7 mg for participants assigned to receive a nominal dose of BLV 2 mg.

Baseline value was the last available value collected on or prior to the first dose of bulevirtide and the last available value collected prior to or at randomization for the BSC arm.

Source: (35, 70)

B.1.4 Alanine aminotransferase normalisation

Table 58 presents the proportion of participants who achieved normalized ALT. At Week 48, the proportion of participants with ALT normalisation in each group was as follows (35):

- BSC arm: 11.8% (95% CI: 4.4%-23.9%)
- Bulevirtide 2 mg arm: 51.0% (95% CI: 36.3%-65.6%)

The differences in proportions of participants with ALT normalisation (95% CI) between the BSC and the bulevirtide 2 mg arms were statistically significant and are as follows:

- Bulevirtide 2 mg arm versus BSC arm: 39.3% (95% CI: 20.0%-55.8%; p < 0.0001)

Table 76 Alanine aminotransferase normalisation by Visit up to Week 240 (Full Analysis Set), Missing = Failure

	BSC[a] (N=51)	Bulevirtide 2 mg (N=49)
Week 24		
Responder, n (%)	3 (5.9%)	26 (53.1%)
95% CI	1.2% to 16.2%	38.3% to 67.5%
Response rate diff vs BSC	-	47.2%
95% CI	-	30.6% to 62.5%
p-value	-	< 0.0001
Week 48		
Responder, n (%)	6 (11.8%)	25 (51.0%)

95% CI	4.4% to 23.9%	36.3% to 65.6%
Response rate diff vs BSC	-	39.3%
95% CI	-	20.0% to 55.8%
p-value	-	< 0.0001
Week 72		
Responder, n (%)	-	26 (53.1%)
95% CI	-	38.3% to 67.5%
Week 96		
Responder, n (%)	-	31 (63.3%)
95% CI	-	48.3% to 76.6%
Week 144		
Responder, n (%)	-	29 (59.2%)
95% CI	-	44.2% to 73.0%
Week 168 (follow-up Week 24)		
Responder, n (%)	-	12 (24.5%)
95% CI	-	13.3% to 38.9%
Week 192 (follow-up Week 48)		
Responder, n (%)	-	13 (26.5%)
95% CI	-	14.9% to 41.1%
Week 240 (follow-up Week 96)		
Responder, n (%)	-	12 (24.5%)
95% CI	-	13.3% to 38.9%

Abbreviations: BSC = best supportive care; CI = confidence interval; diff = difference

[a] From Week 48 through the end of treatment, participants received bulevirtide 10 mg.

The 95% CI for each group was based on the Clopper-Pearson exact method.

Source: (35, 69, 70)

The mean (SD) ALT levels declined rapidly (greatest declines within the first 24 weeks of bulevirtide initiation) and then were generally maintained over the 144-week on-treatment period for the bulevirtide 2 mg. Mean (SD) changes from baseline are summarized in Table 59. In the posttreatment period, mean ALT levels increased in the posttreatment period for the bulevirtide 2 mg arm compared with the on-treatment period (35).

Table 77 Mean (SD) ALT (U/L) (Full Analysis Set), Observed cases

	BSC[a] (N=51)	Bulevirtide 2 mg (N=49)
Baseline		
Mean (SD), U/L	[redacted]	[redacted]
Week 24		
Mean (SD), U/L	[redacted]	[redacted]
Change from baseline, mean (SD)	[redacted]	
Week 48		
Mean (SD), U/L	[redacted]	[redacted]
Change from baseline, mean (SD)	[redacted]	[redacted]
Week 96		[redacted]
Mean (SD), U/L	-	
Change from baseline, mean (SD)	-	
Week 144		
Mean (SD), U/L	-	
Change from baseline, mean (SD)	-	
Week 168 (follow-up Week 24)		
Mean (SD), U/L	-	
Change from baseline, mean (SD)	-	
Week 192 (follow-up Week 48)		
Mean (SD), U/L	-	
Change from baseline, mean (SD)	-	
Week 240 (follow-up Week 96)		
Mean (SD), U/L	-	
Change from baseline, mean (SD)	-	

Abbreviations: BSC = best supportive care; SD = standard deviation

[a] From Week 48 through the end of treatment, participants received bulevirtide 10 mg.

Baseline value was the last available value collected on or prior to the first dose of bulevirtide and the last available value collected prior to or at randomization for the BSC arm.

Source: (35)

B.1.5 Virologic response

As shown in Table 60, the proportions of participants achieving virologic response (HDV RNA decrease by ≥ 2 log10 IU/mL from baseline or undetectable HDV RNA) at Week 48 for the FAS were as follows (35):

- BSC arm: 3.9% (95% CI: 0.5%-13.5%)
- Bulevirtide 2 mg arm: 73.5% (95% CI: 58.9%-85.1%)

The difference in proportion of participants with virologic response (95% CI) at Week 48 between the bulevirtide 2 mg arm and the BSC arm were statistically significant and is as follows:

- Bulevirtide 2 mg arm versus BSC arm: 69.5% (95% CI: 54.1%-81.9%; $p < 0.0001$)

During the on-treatment period, the virologic response rate continuously improved over time for participants receiving bulevirtide 2 mg through 96 weeks of treatment and was maintained from Week 96 to Week 144. In the posttreatment period, the rates decreased in the bulevirtide 2 mg arm through follow-up Week 48, then remained stable through follow-up Week 96 (Table 60) (35).

Table 78 Virologic Response Over Time (Full Analysis Set), Missing = Failure

	BSC[a] (N=51)	Bulevirtide 2 mg (N=49)
Week 24		
Responder, n (%)	2 (3.9%)	27 (55.1%)
95% CI	0.5% to 13.5%	40.2% to 69.3%
Week 48		
Responder, n (%)	2 (4%)	36 (73%)
95% CI	0.5% to 13.5%	58.9% to 85.1%
Response rate diff vs BSC	-	69.5%
95% CI	-	54.1% to 81.9%
p-value	-	< 0.0001
Week 72		
Responder, n (%)	-	34 (69.4%)
95% CI	-	54.6% to 81.7%
Week 96		
Responder, n (%)	-	37 (76%)
95% CI	-	61.1% to 86.7%
Week 144		
Responder, n (%)	-	36 (73.5%)
95% CI	-	58.9% to 85.1%

Week 168 (follow-up Week 24)		
Responder, n (%)	-	19 (38.8%)
95% CI	-	25.2% to 53.8%
Week 192 (follow-up Week 48)		
Responder, n (%)	-	14 (28.6%)
95% CI	-	16.6% to 43.3%
Week 240 (follow-up Week 96)		
Responder, n (%)	-	16 (32.7%)
95% CI	-	19.9% to 47.5%

Abbreviations: BSC = best supportive care; CI = confidence interval; diff = difference

[a] From Week 48 through the end of treatment, participants received bulevirtide 10 mg.

The 95% CI for each group was based on the Clopper-Pearson exact method.

Source: (35, 69, 70)

Figure 23 presents the distribution of virologic response category (as defined as HDV RNA decline by log10 changes from baseline) for the bulevirtide 2 mg arm at Weeks 24, 48, 96, and 144. The majority of participants who achieved virologic response by Week 24 remained virologic responders up to Week 144. The majority of those with partial response at Week 24 shifted to the virologic responder category by Week 144. Approximately half of those who were nonresponders at Week 24 became virologic responders with continued therapy; very few participants remained nonresponders for the entire duration of the treatment period. Overall, continued therapy with bulevirtide through 144 weeks resulted in continuous improvements in virologic response categories throughout the treatment period. Once virologic response was achieved it was maintained in most participants (35).

[redacted]

B.1.6 Change from baseline in liver stiffness

The change from baseline in liver stiffness was a prespecified secondary endpoint for the Week 48 analysis and was the only prespecified secondary efficacy endpoint evaluated at yearly intervals, through Week 240. Decreases in liver stiffness (measured by FibroScan) demonstrate an improvement in the clinical status of the participants, which can represent a decline in liver inflammation as well as improvement of liver fibrosis. Change from baseline in liver stiffness, for the FAS, is presented in Table 61. The LS means (95% CI) of change from baseline at Week 48 in liver stiffness using an ANCOVA model were as follows (35):

- BSC arm: 0.87 kPa (95% CI: −0.79 to 2.53 kPa)
- Bulevirtide 2 mg arm: −3.06 kPa (95% CI: −4.67 to −1.45 kPa)

The difference between the bulevirtide 2 mg arm and the BSC arm in liver stiffness change from baseline at Week 48 was statistically significant and is presented below:

- Bulevirtide 2 mg group versus BSC arm: −3.93 kPa (95% CI: −6.23 to −1.63 kPa; p = 0.0009)

An mixed-effects model for repeated measures (MMRM) model was used to assess the change from baseline at Weeks 96 and 144, and follow-up Weeks 48 and 96 (35).

Table 79 Change from baseline in liver stiffness over time (Full Analysis Set), observed cases

	BSC[a] (N=51)	Bulevirtide 2 mg (N=49)
Week 48		
LS means, kPa	0.9	−3.1
SE of LS means, kPa	0.839	0.814
95% CI	−0.79 to 2.53	−4.7 to −1.5
LS-mean of diff vs BSC	-	−3.93
SE of LS-mean of diff vs BSC	-	1.162
95% CI	-	−6.23 to −1.63
p-value	-	0.0009
Week 96		
LS means, kPa	-	-4.31
95% CI	-	−5.54 to −3.08
Week 144		
LS means, kPa	-	−5.24
95% CI	-	−6.85 to −3.63
Week 192 (follow-up Week 48)		
LS means, kPa	-	−3.74
95% CI	-	−5.28 to −2.20
Week 240 (follow-up Week 96)		
LS means, kPa	-	−1.20
95% CI	-	−3.71 to 1.31

Abbreviations: BSC = best supportive care; CI = confidence interval; diff = difference; kPa = kilopascal; LS = least square; MMRM = mixed-effects model for repeated measure; SE = standard error

[a] From Week 48 through the end of treatment, participants received bulevirtide 10 mg.

The LS-mean, SE, 95% CI, and P value for Week 48 were based on the ANCOVA model for change from baseline with treatment group, region, presence of cirrhosis, and baseline value as covariates. The values for follow up data were based on a MMRM model.

Baseline value was the last available value collected on or prior to the first dose of bulevirtide and the last available value collected prior to or at randomization for the BSC arm.

Source: (35, 70)

B.1.7 Change in fibrosis from baseline

Table 62 presents the change from baseline in fibrosis at Week 48 in the FAS. Fibrosis was assessed by the following parameters (35):

Ishak fibrosis score: Stage 0 (no fibrosis) through Stage 6 (cirrhosis, probable or definite)

Knodell fibrosis score: Stage 0 (no fibrosis) through Stage 4 (cirrhosis)

METAVIR fibrosis stage: F0 (no fibrosis) through F4 (cirrhosis)

In the subset of participants with available data, the percentages of participants who had an improvement (ie, decrease of at least 1 point from baseline) in the fibrosis parameters (Ishak fibrosis score, Knodell fibrosis score, and METAVIR fibrosis stage) at Week 48 were numerically higher in the bulevirtide 2 mg arm compared with the BSC arm. The percentages of participants who had worsening fibrosis parameters were higher in the BSC arm than in the bulevirtide 2 mg arm (35).

Table 80 Change in fibrosis from baseline to Week 48 (Full Analysis Set)

	BSC[a] (N=51)	Bulevirtide 2 mg (N=49)
The stage of liver fibrosis (Ishak)	27	24
Improving	8 (29.6%)	14 (58.3%)
No change	9 (33.3%)	4 (16.7%)
Worsening	10 (37.0%)	6 (25.0%)
The stage of liver fibrosis (Knodell)	27	24
Improving	7 (25.9%)	11 (45.8%)
No change	13 (48.1%)	8 (33.3%)
Worsening	7 (25.9%)	5 (20.8%)
The stage of liver fibrosis (METAVIR)	27	24
Improving	8 (29.6%)	12 (50.0%)
No change	9 (33.3%)	7 (29.2%)
Worsening	10 (37.0%)	5 (20.8%)

Abbreviations: BSC = best supportive care

[a] From Week 48 through the end of treatment, participants received bulevirtide 10 mg.

Baseline value was the last available value collected on or prior to the first dose of bulevirtide and the last available value collected prior to or at randomization for the BSC arm.

Source: (35)

B.1.8 HBsAg response

One patient in the bulevirtide 2 mg arm achieved HBsAg loss with seroconversion by Week 240 (35).

HBsAg response was defined as HBsAg decrease by ≥ 1 log10 IU/mL from baseline. At Week 48 (prior to receiving bulevirtide), the proportion of participants who achieved HBsAg response in the BSC arm was 2.0% (95% CI: 0.0%-10.4%) while no participant in the bulevirtide 2 mg arm had HBsAg response after 48 weeks on bulevirtide treatment. At Week 144, 1 participant (2.0%) in the bulevirtide 2 mg arm achieved HBsAg response. In the posttreatment period, at follow-up Week 96, 4 participants (8.2%) in the bulevirtide 2 mg arm achieved HBsAg response (35).

Summary statistics for the absolute values and change from baseline in HBsAg levels (log10 IU/mL scale) through Week 240 (follow-up Week 96) are provided in Table 63. The mean (SD) of changes from baseline for HBsAg levels while on treatment at Weeks 48, 96, and 144 were minimal across the bulevirtide 2 mg and BSC arm. During the posttreatment period, mean (SD) of changes from baseline for HBsAg were slightly decreased through follow-up Week 96 for the bulevirtide 2 mg arm (35).

Table 81 HBsAg (log10 IU/mL) change from baseline by visit up to Week 240 (Full Analysis Set)

	BSC[a] (N=51)	Bulevirtide 2 mg (N=49)
Baseline		
N	51	47
Mean (SD), log10 IU/mL	3.68 (0.465)	3.67 (0.515)
Median	3.75	3.75
Q1, Q3	3.51, 4.00	3.48, 4.00
Min, max	2.53, 4.43	2.32, 4.48
Change from Baseline at Week 48		
N	50	46
Mean (SD), log10 IU/mL	0.01 (0.380)	0.09 (0.202)
Median	0.06	0.12
Q1, Q3	-0.09, 0.19	-0.04, 0.22
Min, max	-2.21, 0.61	-0.48, 0.48
Change from Baseline at Week 96		
N	-	45
Mean (SD), log10 IU/mL	-	-0.20 (0.261)
Median	-	-0.15
Q1, Q3	-	-0.35, 0.00
Min, max	-	-0.78, 0.19

Change from Baseline at Week 144		
N	-	43
Mean (SD), log10 IU/mL	-	-0.36 (0.596)
Median	-	-0.24
Q1, Q3	-	-0.40, -0.05
Min, max	-	-3.74, 0.09
Change from Baseline at Week 192 (follow-up Week 48)		
N	-	33
Mean (SD), log10 IU/mL	-	-0.41 (0.803)
Median	-	-0.18
Q1, Q3	-	-0.37, -0.05
Min, max	-	-4.34, 0.20
Change from Baseline at Week 240 (follow-up Week 96)		
N	-	27
Mean (SD), log10 IU/mL	-	-0.54 (0.962)
Median	-	-0.24
Q1, Q3	-	-0.74, -0.02
Min, max	-	-4.34, 0.41

Abbreviations: BSC = best supportive care; Q1/Q3 = first/third quartile; SD = standard deviation

[a] From Week 48 through the end of treatment, participants received bulevirtide 10 mg.

Baseline value was the last available value collected on or prior to the first dose of bulevirtide and the last available value collected prior to or at randomization for the BSC arm.

Source: (35, 69, 70)

B.1.9 Liver-related clinical events

From baseline through Week 144, there [redacted] (development of nonserious [redacted]) that occurred in a participant with cirrhosis in the BSC to bulevirtide 10 mg group, 165 days after switching to bulevirtide 10 mg treatment. Through Week 144, there [redacted] not associated with any AE reported in one participant in the bulevirtide 2 mg group. This was a planned [redacted], and the participant had medical history of this condition (Table 82) (35). During the posttreatment period, there were [redacted] in the bulevirtide 2 mg group [redacted] the bulevirtide 10 mg group ([redacted] nonserious [redacted]), and [redacted] in the

BSC to bulevirtide 10 mg group [redacted] During the posttreatment period, [redacted] participants [redacted] in the bulevirtide 2 mg group (due to [redacted] and [redacted]) and [redacted] in the BSC to bulevirtide 10 mg group (due to [redacted] Table 82) (35).

Table 64 Potential liver-related clinical events (Full Analysis Set)

	BSC (N=51)	Bulevirtide 2 mg (N=49)	Bulevirtide 10 mg (N=50)	Bulevirtide BSC to 10 mg (N=50)
Participants with any potential liver-related clinical event. n (%; 95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Week 48, n (%)				
Liver-related hospitalisation	[redacted]	[redacted]	[redacted]	N/A
Week 48 to Week 144, n (%)				
Ascites	N/A	[redacted]	[redacted]	[redacted]
Week 144 to Week 240, n (%)				
Oesophageal varices haemorrhage	N/A	[redacted]	[redacted]	[redacted]
Hepatocellular carcinoma	N/A	[redacted]	[redacted]	[redacted]
Hepatic encephalopathy	N/A	[redacted]	[redacted]	[redacted]
Ascites	N/A	[redacted]	[redacted]	[redacted]
Liver-related hospitalisation	N/A	[redacted]	[redacted]	[redacted]

Abbreviations: BSC = best supportive care; N/A = not applicable

Source: (35)

B.1.10 Endpoints by cirrhosis status

Improvements in response rates for combined response (Table 64), ALT normalisation (Table 65), virologic response (Table 66) and undetectable HDV RNA (Table 67) were consistently observed in both subgroups with and without cirrhosis while participants were receiving bulevirtide treatment through Week 144. Rates decreased in the posttreatment period, but there were no consistent trends observed for rates of combined response, virologic response, ALT normalisation, or undetectable HDV RNA over time based on cirrhosis status. The presence of cirrhosis did not appear to meaningfully impact those rates (35).

Table 82 Combined response by Visit up to Week 240 by Cirrhosis Status (Full Analysis Set), Missing = Failure

	BSC[a] (N=51)		Bulevirtide 2 mg (N=49)	
	Cirrhosis status			
	Presence	Absence	Presence	Absence
Week 48, n	24	27	23	26
Responder	1 (4.2%)	0	8 (34.8%)	14 (53.8%)
95% CI	0.1% to 21.1%	0.0% to 12.8%	16.4% to 57.3%	33.4% to 73.4%
Week 96, n	24	27	23	26
Responder	-	-	12 (52.2%)	15 (57.7%)
95% CI	-	-	30.6% to 73.2%	36.9% to 76.6%
Week 144, n	24	27	23	26
Responder	-	-	14 (60.9%)	14 (53.8%)
95% CI	-	-	38.5% to 80.3%	33.4% to 73.4%
Week 192 (follow-up Week 48), n	24	27	23	26
Responder	-	-	4 (17.4%)	7 (26.9%)
95% CI	-	-	5.0% to 38.8%	11.6% to 47.8%
Week 240 (follow-up Week 96), n	24	27	23	26
Responder	-	-	4 (17.4%)	8 (30.8%)
95% CI	-	-	5.0% to 38.8%	14.3% to 51.8%

Abbreviations: BSC = best supportive care; CI = confidence interval

The 95% confidence interval (CI) was based on the Clopper-Pearson exact method. For missing values, the missing equals failure (MEF) approach was used.

Source: (35, 69, 70)

Table 83 ALT normalisation by Visit up to Week 240 by Cirrhosis Status (Full Analysis Set), Missing = Failure

	BSC[a] (N=51)		Bulevirtide 2 mg (N=49)	
	Cirrhosis status			
	Presence	Absence	Presence	Absence
Week 48, n	24	27	23	26
Responder	4 (16.7%)	2 (7.4%)	9 (39.1%)	16 (61.5%)
95% CI	4.7% to 37.4%	0.9% to 24.3%	19.7% to 61.5%	40.6% to 79.8%
Week 96, n	24	27	23	26
Responder	-	-	14 (60.9%)	17 (65.4%)
95% CI	-	-	38.5% to 80.3%	44.3% to 82.8%
Week 144, n	24	27	23	26
Responder	-	-	15 (65.2%)	14 (53.8%)
95% CI	-	-	42.7% to 83.6%	33.4% to 73.4%
Week 192 (follow-up Week 48), n	24	27	23	26
Responder	-	-	6 (26.1%)	7 (26.9%)
95% CI	-	-	10.2% to 48.4%	11.6% to 47.8%
Week 240 (follow-up Week 96), n	24	27	23	26
Responder	-	-	4 (17.4%)	8 (30.8%)
95% CI	-	-	5.0% to 38.8%	14.3% to 51.8%

Abbreviations: ALT = alanine aminotransferase; BSC = best supportive care; CI = confidence interval

The 95% confidence interval (CI) was based on the Clopper-Pearson exact method. For missing values, the missing equals failure (MEF) approach was used.

Source: (35, 69, 70)

Table 84 Virologic response by visit up to Week 240 by cirrhosis status (Full Analysis Set), Missing = Failure

	BSC[a] (N=51)		Bulevirtide 2 mg (N=49)	
	Cirrhosis status			
	Presence	Absence	Presence	Absence
Week 48, n	24	27	23	26

Responder	2 (8%)	0	19 (82.6%)	17 (65%)
95% CI	1.0% to 27.0%	0.0% to 12.8%	61.2% to 95.0%	44.3% to 82.8%
Week 96, n	24	27	23	26
Responder	-	-	19 (83%)	18 (69%)
95% CI	-	-	61.2% to 95.0%	48.2% to 85.7%
Week 144, n	24	27	23	26
Responder	-	-	19 (82.6%)	17 (65.4%)
95% CI	-	-	61.2% to 95.0%	44.3% to 82.8%
Week 192 (follow-up Week 48), n	24	27	23	26
Responder	-	-	7 (30.4%)	7 (26.9%)
95% CI	-	-	13.2% to 52.9%	11.6% to 47.8%
Week 240 (follow-up Week 96), n	24	27	23	26
Responder	-	-	7 (30.4%)	9 (34.6%)
95% CI	-	-	13.2% to 52.9%	17.2% to 55.7%

Abbreviations: BSC = best supportive care; CI = confidence interval

The 95% confidence interval (CI) was based on the Clopper-Pearson exact method. For missing values, the missing equals failure (MEF) approach was used.

Virologic response: Undetectable (< LLOQ, target not detected) HDV RNA or HDV RNA decreased >= 2 log10 IU/mL from baseline.

Source: (35, 69, 70)

Table 85 Undetectable HDV RNA by visit up to Week 240 by cirrhosis status (Full Analysis Set), Missing = Failure

	BSC[a] (N=51)		Bulevirtide 2 mg (N=49)	
	Cirrhosis status			
	Presence	Absence	Presence	Absence
Week 48, n	24	27	23	26
Responder	0	0	5 (21.7%)	1 (3.8%)
95% CI	0.0% to 14.2%	0.0% to 12.8%	7.5% to 43.7%	0.1% to 19.6%
Week 96, n	24	27	23	26
Responder	-	-	6 (26.1%)	4 (15.4%)

95% CI	-	-	10.2% to 48.4%	4.4% to 34.9%
Week 144, n	24	27	23	26
Responder	-	-	8 (34.8%)	6 (23.1%)
95% CI	-	-	16.4% to 57.3%	9.0% to 43.6%
Week 192 (follow-up Week 48), n	24	27	23	26
Responder	-	-	5 (21.7%)	3 (11.5%)
95% CI	-	-	7.5% to 43.7%	2.4% to 30.2%
Week 240 (follow-up Week 96), n	24	27	23	26
Responder	-	-	6 (26.1%)	4 (15.4%)
95% CI	-	-	10.2% to 48.4%	4.4% to 34.9%

Abbreviations: BSC = best supportive care; CI = confidence interval; HDV = hepatitis delta virus

The 95% confidence interval (CI) was based on the Clopper-Pearson exact method. For missing values, the missing equals failure (MEF) approach was used.

Source: (35, 69)

Improvements in liver stiffness were observed while participants were receiving bulevirtide treatment in subgroups with and without cirrhosis. Mean change from baseline in liver stiffness was numerically higher in subgroups with cirrhosis. The greater declines from baseline in liver stiffness in the subgroup with cirrhosis is likely due to the expectedly higher mean liver stiffness at baseline in participants with cirrhosis (Table 68) (35).

Table 86 Liver stiffness (kPa) change from baseline by visit up to Week 240 by cirrhosis status (Full Analysis Set), observed cases

	BSC[a] (N=51)		Bulevirtide 2 mg (N=49)	
	Cirrhosis status			
	Presence	Absence	Presence	Absence
Baseline				
N	24	27	23	26
Mean (SD), kPa	20.05 (9.798)	11.00 (5.386)	19.55 (8.661)	9.07 (3.031)
Median	18.70	9.70	17.60	9.05
Q1, Q3	12.75, 22.55	8.00, 11.90	13.30, 23.40	6.40, 11.40
Min, max	6.20, 41.60	5.80, 32.80	7.80, 46.40	4.30, 15.40
Change from baseline at Week 48				
N	21	25	23	25

Mean (SD), kPa	1.78 (10.106)	-0.20 (4.001)	-5.70 (6.938)	-0.35 (2.084)
Median	0.70	0.20	-4.30	-0.80
Q1, Q3	-2.10, 5.80	-1.40, 1.20	-7.40, -1.80	-2.00, 0.70
Min, max	-17.20, 33.20	-9.70, 10.30	-26.10, 5.80	-3.10, 5.60
Change from baseline at Week 96				
N	-	-	23	24
Mean (SD), kPa	-	.	-6.33 (7.821)	-1.56 (2.474)
Median	.	.	-5.00	-1.50
Q1, Q3	.	.	-9.40, -3.00	-2.55, 0.15
Min, max	-	-	-28.10, 12.90	-9.63, 3.10
Change from baseline at Week 144				
N	-	-	22	23
Mean (SD), kPa	-	-	-8.12 (9.136)	-1.89 (2.666)
Median	-	-	-5.80	-1.60
Q1, Q3	-	-	-10.50, -4.30	-4.00, -0.40
Min, max	-	-	-41.00, 6.10	-6.60, 3.60
Change from baseline at Week 192 (follow-up Week 48)				
N	-	-	17	18
Mean (SD), kPa	-	-	-7.22 (8.441)	-0.06 (3.415)
Median	-	-	-6.40	-0.95
Q1, Q3	-	-	-8.80, -2.10	-2.20, 1.10
Min, max	-	-	-33.00, 2.80	-4.30, 9.00
Change from baseline at Week 240 (follow-up Week 96)				
N	-	-	13	15
Mean (SD), kPa	-	-	-2.22 (13.264)	-0.40 (3.983)
Median	-	-	-4.70	-1.00
Q1, Q3	-	-	-8.40, -3.70	-3.10, 1.00

Min, max	-	-	-22.10, 26.30	-5.60, 10.30

Abbreviations: BSC = best supportive care; kPa = kilopascal; Q1/Q3 = first/third quartile; SD = standard deviation

[a] From Week 48 through the end of treatment, participants received bulevirtide 10 mg.

Baseline value was the last available value collected on or prior to the first dose of bulevirtide and the last available value collected prior to or at randomization for the BSC arm.

Source: (35)

Appendix C. Comparative analysis of efficacy

Not applicable for this application.

Table 87 Comparative analysis of studies comparing [intervention] to [comparator] for patients with [indication]

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
Example: median overall survival		NA	NA	NA	HR: 0.70	0.55–0.90	0.005	The HRs for the studies included were synthesized using random effects meta-analysis (DerSimonian–Laird).	Yes/No
Example: 1-year survival		10.7	2.39–19.01	0.01	HR: 0.70	0.55–0.90	0.005	The HRs for the studies included were synthesized using random effects meta-analysis (DerSimonian–Laird). The absolute difference was estimated by applying the resulting HR to an assumed 1-year survival rate of 64.33% in the comparator group.	

Example: HRQoL	**−4.5**	−8.97 to −0.03	0.04	NA	NA	NA	HRQoL results for the studies included were synthesized using the standardized mean difference (SMD). The estimated meta-analytical SMD of −0.3 (95% CI −2.99 to −0.01) was transformed to the scale of ZZZ* assuming a population standard deviation of 15 on the ZZZ* scale. *Fill in the name of an appropriate measure of HRQoL.
Insert outcome 4							

Appendix D. Extrapolation

Not applicable for this application.

D.1 Extrapolation of [effect measure 1]

D.1.1 Data input

D.1.2 Model

D.1.3 Proportional hazards

D.1.4 Evaluation of statistical fit (AIC and BIC)

D.1.5 Evaluation of visual fit

D.1.6 Evaluation of hazard functions

D.1.7 Validation and discussion of extrapolated curves

D.1.8 Adjustment of background mortality

D.1.9 Adjustment for treatment switching/cross-over

D.1.10 Waning effect

D.1.11 Cure-point

D.2 Extrapolation of [effect measure 2]

Appendix E. Serious adverse events

Below, all SAEs are listed in Table 70 and Table 71.

Table 88 Treatment-emergent SAEs while on treatment by SOC and PT (MYR301 Safety Analysis Set)

System Organ Class Preferred Term	Baseline to Week 48		Baseline to Week 144
	BSC (N=49)[a]	Bulevirtide 2 mg (N=49)	Bulevirtide 2 mg (N=49)

Number (%) of participants with any treatment-emergent SAEs	1 (2.0%)	2 (4.1%)	3 (6.1%)
Gastrointestinal disorders	0	0	1 (2.0%)
Varices oesophageal			
Hepatobiliary disorders	1 (2.0%)	0	0
Cholelithiasis	1 (2.0%)	0	0
Infections and infestations	1 (2.0%)	0	0
COVID-19	1 (2.0%)	0	0
Injury, poisoning and procedural complications	0	1 (2.0%)	1 (2.0%)
Foot fracture	0	1 (2.0%)	1 (2.0%)
Nervous system disorders	0	1 (2.0%)	1 (2.0%)
Headache	0	1 (2.0%)	1 (2.0%)
Hemiparesis	0	1 (2.0%)	1 (2.0%)
Psychiatric disorders	0	1 (2.0%)	1 (2.0%)
Depression	0	1 (2.0%)	1 (2.0%)

Abbreviations: AE = adverse event; BSC = best supportive care; COVID-19 = coronavirus disease 2019; DT = delayed treatment; PT = preferred term; SAE = serious adverse event; SOC = system organ class

[a] From Week 48 through the end of treatment, participants received bulevirtide 10 mg.

Adverse events were coded according to MedDRA Version 27.1.

For bulevirtide 2 mg, treatment-emergent events "while on treatment" began on or after the first dose of bulevirtide up to the last dose of bulevirtide study drug or led to premature discontinuation of bulevirtide. For the BSC group, included AEs began on or after the randomization date and prior to bulevirtide first dose, or up to early termination date if the participant discontinued the study before Week 48 visit. The AEs were allocated to periods based on event onset dates. Multiple adverse events reported in a participant with the same SOC and PT were counted only once for the SOC and PT. SOCs were presented alphabetically and PTs within SOC were presented in descending order for the BLV 2 mg (baseline to Week 144) frequencies.

Source: Gilead Sciences Inc. (35)

Table 89 SAEs by PT in the posttreatment period up to follow-up Week 96 (MYR301 Posttreatment Safety Analysis Set)

Preferred term	Bulevirtide 2 mg (N=46)
Number (%) of Participants with Any SAEs	7 (15.2%)
Hepatitis D	4 (8.7%)
Anaemia	1 (2.2%)
Hepatitis acute	1 (2.2%)
Hepatocellular carcinoma	1 (2.2%)
Oesophageal varices haemorrhage	1 (2.2%)

Abbreviations: PT = preferred term; SAE = serious adverse event

Adverse events were coded according to MedDRA Version 27.1.

Adverse events with an onset date after the last dose date of BLV were included in this summary. Multiple AEs were counted only once per participant and PT.

Source: Gilead Sciences Inc. (35)

Appendix F. Health-related quality of life

Not applicable for this application.

Appendix G. Probabilistic sensitivity analyses

[redacted]

Table 90 Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Probabilities and HRs				
TP - RNA+ - Fx to Fx+1	0,150722	0,13596	0,166096	Beta
TP - RNA+ - F0-F2 to HCC	0,013789	0,012444	0,015201	Beta
TP - RNA+ - F3 to HCC	0,013789	0,012444	0,015201	Beta
TP - RNA+ - CC (F4) to DC	0,106711	0,096274	0,117611	Beta
TP - RNA+ - CC (F4) to HCC	0,062421	0,056324	0,068805	Beta
TP - RNA+ - CC (F4) to Death	0,072631	0,065535	0,080057	Beta
TP - RNA+ - DCC to HCC	0,078284	0,070634	0,086287	Beta
TP - RNA+ - DCC to LT	0,0155	0,013988	0,017087	Beta
TP - RNA+ - DCC to Death	0,156	0,140718	0,171909	Beta
TP - RNA+ - HCC to LT	0,0155	0,013988	0,017087	Beta
TP - RNA+ - HCC to Death	0,56	0,503664	0,615581	Beta

TP - RNA+ - LT to Death	0,21	0,189386	0,231374	Beta
TP - RNA+ - Post-LT to Death	0,057	0,051433	0,062831	Beta
TP - Spontaneous Clearance	0,0113	0,009206	0,013602	Beta
W24 Resp Efficacy - HEPCLUDEX	0,367	0,233887	0,51135	Beta
W24 Subopt Resp Efficacy - HEPCLUDEX	0	0	0	Beta
W24 Resp Efficacy - BSC	0	0	0	Beta
W24 Subopt Resp Efficacy - BSC	0	0	0	Beta
W48 Resp Efficacy - HEPCLUDEX	0,449	0,30645	0,595956	Beta
W48 Subopt Resp Efficacy - HEPCLUDEX	0	0	0	Beta
W48 Resp Efficacy - BSC	0,02	0,018049	0,022048	Beta
W48 Subopt Resp Efficacy - BSC	0	0	0	Beta
W72 Resp Efficacy - HEPCLUDEX	0,449	0,30645	0,595956	Beta
W72 Subopt Resp Efficacy - HEPCLUDEX	0	0	0	Beta
W96 Resp Efficacy - HEPCLUDEX	0,551	0,415553	0,682714	Beta
W96 Subopt Resp Efficacy - HEPCLUDEX	0	0	0	Beta
W120 Resp Efficacy - HEPCLUDEX	0,571	0,435456	0,701345	Beta
W120 Subopt Resp Efficacy - HEPCLUDEX	0	0	0	Beta
W144 Resp Efficacy - HEPCLUDEX	0,571	0,435456	0,701345	Beta
W144 Subopt Resp Efficacy - HEPCLUDEX	0	0	0	Beta

W72 Resp Efficacy - BSC	0,02	0,0180 49	0,0220 48	Beta
W72 Subopt Resp Efficacy - BSC	0	0	0	Beta
W96 Resp Efficacy - BSC	0,02	0,0180 49	0,0220 48	Beta
W96 Subopt Resp Efficacy - BSC	0	0	0	Beta
Discon - HEPCLUDEX	0	0	0	Beta
Discon - BSC	0	0	0	Beta
HR Resp HEPCLUDEX - Fx to Fx+1	0,2202 23	0,0628 35	0,4745	Gamma
HR Resp HEPCLUDEX - F0-F2 to HCC	0,3367	0,1954 34	0,5157 61	Gamma
HR Resp HEPCLUDEX - F3 to HCC	0,3367	0,1954 34	0,5157 61	Gamma
HR Resp HEPCLUDEX - CC (F4) to DC	0,2202 23	0,0421 77	0,5425	Gamma
HR Resp HEPCLUDEX - CC (F4) to HCC	0,3367	0,1954 34	0,5157 61	Gamma
HR Resp HEPCLUDEX - CC (F4) to Death	0,2645 5	0,1342 8	0,4382 49	Gamma
HR Resp HEPCLUDEX - DCC to HCC	1	0	0	Gamma
HR Resp HEPCLUDEX - DCC to LT	1	0	0	Gamma
HR Resp HEPCLUDEX - DCC to Death	1	0	0	Gamma
HR Resp HEPCLUDEX - HCC to LT	1	0	0	Gamma
HR Resp HEPCLUDEX - HCC to Death	1	0	0	Gamma
HR Resp HEPCLUDEX - LT to Death	1	0	0	Gamma
HR Resp HEPCLUDEX - Post-LT to Death	1	0	0	Gamma
HR Resp HEPCLUDEX - Spontaneous Clearance	1	0	0	Gamma

HR Resp BSC - Fx to Fx+1	0,220223	0,198749	0,242783	Gamma
HR Resp BSC - F0-F2 to HCC	0,3367	0,303869	0,371192	Gamma
HR Resp BSC - F3 to HCC	0,3367	0,303869	0,371192	Gamma
HR Resp BSC - CC (F4) to DC	0,220223	0,198749	0,242783	Gamma
HR Resp BSC - CC (F4) to HCC	0,3367	0,303869	0,371192	Gamma
HR Resp BSC - CC (F4) to Death	0,26455	0,238754	0,291651	Gamma
HR Resp BSC - DCC to HCC	1	0,90249	1,10244	Gamma
HR Resp BSC - DCC to LT	1	0,90249	1,10244	Gamma
HR Resp BSC - DCC to Death	1	0,90249	1,10244	Gamma
HR Resp BSC - HCC to LT	1	0,90249	1,10244	Gamma
HR Resp BSC - HCC to Death	1	0,90249	1,10244	Gamma
HR Resp BSC - LT to Death	1	0,90249	1,10244	Gamma
HR Resp BSC - Post-LT to Death	1	0,90249	1,10244	Gamma
HR Resp BSC - Spontaneous Clearance	1	0,90249	1,10244	Gamma
HR Subopt Resp HEPCLUDEX - Fx to Fx+1	1	0,90249	1,10244	Gamma
HR Subopt Resp HEPCLUDEX - F0-F2 to HCC	1	0,90249	1,10244	Gamma
HR Subopt Resp HEPCLUDEX - F3 to HCC	1	0,90249	1,10244	Gamma

HR Subopt Resp HEPCLUDEX - CC (F4) to DC	1	0,90249	1,10244	Gamma
HR Subopt Resp HEPCLUDEX - CC (F4) to HCC	1	0,90249	1,10244	Gamma
HR Subopt Resp HEPCLUDEX - CC (F4) to Death	1	0,90249	1,10244	Gamma
HR Subopt Resp HEPCLUDEX - DCC to HCC	1	0,90249	1,10244	Gamma
HR Subopt Resp HEPCLUDEX - DCC to LT	1	0,90249	1,10244	Gamma
HR Subopt Resp HEPCLUDEX - DCC to Death	1	0,90249	1,10244	Gamma
HR Subopt Resp HEPCLUDEX - HCC to LT	1	0,90249	1,10244	Gamma
HR Subopt Resp HEPCLUDEX - HCC to Death	1	0,90249	1,10244	Gamma
HR Subopt Resp HEPCLUDEX - LT to Death	1	0,90249	1,10244	Gamma
HR Subopt Resp HEPCLUDEX - Post-LT to Death	1	0,90249	1,10244	Gamma
HR Subopt Resp HEPCLUDEX - Spontaneous Clearance	1	0,90249	1,10244	Gamma
HR Subopt Resp BSC - Fx to Fx+1	1	0,90249	1,10244	Gamma
HR Subopt Resp BSC - F0-F2 to HCC	1	0,90249	1,10244	Gamma
HR Subopt Resp BSC - F3 to HCC	1	0,90249	1,10244	Gamma
HR Subopt Resp BSC - CC (F4) to DC	1	0,90249	1,10244	Gamma
HR Subopt Resp BSC - CC (F4) to HCC	1	0,90249	1,10244	Gamma
HR Subopt Resp BSC - CC (F4) to Death	1	0,90249	1,10244	Gamma

HR Subopt Resp BSC - DCC to HCC	1	0,90249	1,10244	Gamma
HR Subopt Resp BSC - DCC to LT	1	0,90249	1,10244	Gamma
HR Subopt Resp BSC - DCC to Death	1	0,90249	1,10244	Gamma
HR Subopt Resp BSC - HCC to LT	1	0,90249	1,10244	Gamma
HR Subopt Resp BSC - HCC to Death	1	0,90249	1,10244	Gamma
HR Subopt Resp BSC - LT to Death	1	0,90249	1,10244	Gamma
HR Subopt Resp BSC - Post-LT to Death	1	0,90249	1,10244	Gamma
HR Subopt Resp BSC - Spontaneous Clearance	1	0,90249	1,10244	Gamma
AE HEPCLUDEX - Neutropenia	0	0	0	Beta
AE HEPCLUDEX - Thrombocytopenia	0,020408	0,018417	0,022498	Beta
AE HEPCLUDEX - Leukopenia	0	0	0	Beta
AE BSC - Neutropenia	0,039216	0,035388	0,043229	Beta
AE BSC - Thrombocytopenia	0,0588	0,053057	0,064814	Beta
AE BSC - Leukopenia	0,019608	0,017695	0,021616	Beta
FibReg - Resp - CC(F4) to F3 - HEPCLUDEX	0,317591	0,28627	0,349768	Beta
FibReg - Resp - F2 to F1 - HEPCLUDEX	0,087635	0,079069	0,096591	Beta
FibReg - SubOpt Resp - CC(F4) to F3 - HEPCLUDEX	0	0	0	Beta
FibReg - SubOpt Resp - F2 to F1 - HEPCLUDEX	0	0	0	Beta

FibReg - Resp - CC(F4) to F3 - BSC	0,317591	0,28627	0,349768	Beta
FibReg - Resp - F2 to F1 - BSC	0,087635	0,079069	0,096591	Beta
FibReg - SubOpt Resp - CC(F4) to F3 - BSC	0	0	0	Beta
FibReg - SubOpt Resp - F2 to F1 - BSC	0	0	0	Beta
Costs				
HCRU - HEP - Tx Init - F0-F3 - Outpatient visits	4	3,609959	4,409762	Gamma
HCRU - HEP - Tx Init - F4 - outpatient visits	4	3,609959	4,409762	Gamma
HCRU - HEP - On Tx - F0-F3 - outpatient visits	6	5,414938	6,614642	Gamma
HCRU - HEP - On Tx - F4 - outpatient Visits	8	7,219918	8,819523	Gamma
HCRU - Off Tx / BSC - F0-F3 - outpatient Visits	2	1,804979	2,204881	Gamma
HCRU - Off Tx / BSC - CC - Outpatient Visits	6	5,414938	6,614642	Gamma
HEPCLUDEX - Adherence	1	0	0	Beta
Continous management - DCC - annual outpatient visits	6	5,414938	6,614642	Gamma
Continous management - DCC - annual inpatient visits	2	1,804979	2,204881	Gamma
Continous management - HCC - annual outpatient visits	4	3,609959	4,409762	Gamma
Continous management - HCC - annual inpatient visits	3	2,707469	3,307321	Gamma
Continous management - PLT - annual outpatient visits	4	3,609959	4,409762	Gamma
Continous management - PLT - annual inpatient visits	1,33	1,200311	1,466246	Gamma

One-off costs: transplant	932526	841595,1	1028054	Gamma
Patient time - outpatient visit - admin training	1	0,90249	1,10244	Gamma
Patient time - outpatient visit - disease management	1	0,90249	1,10244	Gamma
Patient time - inpatient visit (DCC) - disease management	120	108,2988	132,2928	Gamma
Patient time - inpatient visit (HCC) - disease management	168	151,6183	185,21	Gamma
Patient time - inpatient visit (PLT) - disease management	168	151,6183	185,21	Gamma
Patient time - inpatient visit (LT) - disease management	168	151,6183	185,21	Gamma
Two-way travels - outpatient visit - admin training	1	0,90249	1,10244	Gamma
Two-way travels - outpatient visit - disease management	1	0,90249	1,10244	Gamma
Two-way travels - inpatient visit (DCC) - disease management	1	0,90249	1,10244	Gamma
Two-way travels - inpatient visit (HCC) - disease management	1	0,90249	1,10244	Gamma
Two-way travels - inpatient visit (PLT) - disease management	1	0,90249	1,10244	Gamma
Two-way travels - inpatient visit (LT) - disease management	1	0,90249	1,10244	Gamma
Population				
Patient Distribution - F0	0	0	0	Beta
Patient Distribution - F1	0	0	0	Beta
Patient Distribution - F2	0,489	0,440179	0,537925	Beta
Patient Distribution - F3	0,104	0,093829	0,114624	Beta

HSUV				
Utility - Non Resp - F0	0,918	0,870205	0,955646	Beta
Utility - Non Resp - F1	0,871	0,840666	0,898592	Beta
Utility - Non Resp - F2	0,853	0,822321	0,88126	Beta
Utility - Non Resp - F3	0,881	0,823201	0,928686	Beta
Utility - Non Resp - CC (F4)	0,84	0,721556	0,93021	Beta
Utility - Subopt Resp - F0	0,918	0,870205	0,955646	Beta
Utility - Subopt Resp - F1	0,871	0,840666	0,898592	Beta
Utility - Subopt Resp - F2	0,853	0,822321	0,88126	Beta
Utility - Subopt Resp - F3	0,881	0,823201	0,928686	Beta
Utility - Subopt Resp - CC (F4)	0,84	0,721556	0,93021	Beta
Utility - Resp - F0	0,959	0,900757	0,992107	Beta
Utility - Resp - F1	0,912	0,85294	0,957056	Beta
Utility - Resp - F2	0,894	0,836136	0,940514	Beta
Utility - Resp - F3	0,822	0,745783	0,887193	Beta
Utility - Resp - CC (F4)	0,881	0,753211	0,965894	Beta
Utility - DCC	0,501181	0,466404	0,535953	Beta

Utility - HCC	0,609398	0,401147	0,798495	Beta
Utility - LT	0,671237	0,628054	0,713033	Beta
Utility - PLT	0,748535	0,708938	0,786182	Beta
AE Disutility - Neutropenia	0,0144	0,012995	0,015875	Beta
AE Disutility - Thrombocytopenia	0,0144	0,012995	0,015875	Beta
AE Disutility - Leukopenia	0,0144	0,012995	0,015875	Beta

Abbreviations: AE = adverse event; BSC = best supportive care; CC = compensated cirrhosis; DCC = decompensated cirrhosis; F1-4 = fibrosis stage 1-4; HCC = hepatocellular carcinoma; HCRU = healthcare resources utilisation; HEP = Hepcludex; HR = hazard ratio; HSUV = health state utility value; LT = liver transplant; PLT = post-liver transplant; RNA = ribonucleic acid; TP = transition probability; W = week

Appendix H. Literature searches for the clinical assessment

H.1 Efficacy and safety of the intervention and comparator(s)

A thorough SLR was conducted starting in October 2020 to ensure a complete and updated understanding of bulevirtide for clinical assessment, focusing on its efficacy and safety for patients according to the indication. Furthermore, multiple updated SLRs were performed in April 2021, December 2021, and July 2024. The process followed established practices and was comprised of the following core stages: definition of scope and agreement of search terms, implementation of searches and abstract review to inform included papers, and extraction and quality assessment of data.

Relevant studies were identified by searching the key biomedical databases suggested by the Health technology assessment (HTA) agencies such as National Institute for Health and Care Excellence (NICE). The key biomedical databases include (Table 73):

- Embase®
- MEDLINE®
- MEDLINE® In-Process
- Cochrane Central Register of Controlled Trials (CENTRAL)
- Cochrane Database of Systematic Reviews (CDSR)
- National health service economic evaluation database (NHS EED-updated until 2014-15) (searched using the National Institute for Health and Care Research (NIHR) Centre for Reviews and Dissemination (CRD) interface)
- Health Technology Assessments (HTA) database and country-specific HTA searching

Throughout the updates, all databases were searched from inception till July 2024 to retrieve the most recent evidence. Search strategies for Embase® were implemented using the embase.com platform, MEDLINE® using the PubMed platform, CENTRAL using the Wiley Online platform and NHS-EED using the CRD, University of York Online platform. Conference proceedings were searched via Embase or by screening the conference for the last three years (starting 2018 for the original SLR) to include the latest clinical studies, which have not yet been published in journals as full-text articles. Updated manual hand searches of conference proceedings were conducted to identify any further relevant abstracts. The relevant conferences for abstract screening included (Table 75):

- American Association of Liver Diseases (AASLD) https://aasldpubs.onlinelibrary.wiley.com/journal/15273350
- European Association for the study of Liver Diseases (EASL) https://www.journal-of-hepatology.eu/

- International Liver Congress
- European Congress for Clinical Microbiology and Infectious Diseases (ECCMID) https://www.escmid.org/
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR) https://www.ispor.org/heor-resources/presentations-database/search
- American Transplant Congress meeting abstracts: https://atcmeetingabstracts.com/
- American Society of Clinical Oncology (ASCO) American Society of Clinical Oncology - ASCO
- American Society of Hematology (ASH) American Society of Hematology - Hematology.org

To identify clinical studies which have taken place or are taking place, a review of the following clinical trial information sites was performed (Table 74):

- Clinicaltrials.gov: http://www.clinicaltrials.gov/
- International Clinical Trials Registry Platform (ICTRP): https://www.who.int/ictrp/en/
- EU Clinical Trials Register: https://www.clinicaltrialsregister.eu/
- PharmNet.Bund: https://www.pharmnet-bund.de/static/en/clinical-trials/index.html
- German Clinical Trials Register https://www.bfarm.de/EN/BfArM/Tasks/German-Clinical-Trials-Register/
- International Standard Randomised Controlled Trial Number (ISRCTN) Registry ISRCTN Registry

Additionally, previous submission documentation from the following HTA bodies was reviewed for relevant data (Table 74):

- National Institute for Health and Care Excellence (NICE): http://www.nice.org.uk/
- Scottish Medicines Consortium (SMC): http://scottishmedicines.org.uk
- All Wales Medicines Strategy Group (AWMSG): https://www.gov.wales/all-wales-medicines-strategy-group
- German Institute for Quality and Efficiency in Health Care (IQWiG): https://www.iqwig.de/
- Gemeinsamer Bundesausschuss (The Federal Joint Committee [G-BA]):https://www.g-ba.de/
- Institute for Clinical and Economic Review (ICER): https://icer-review.org/
- Pharmaceutical Benefits Advisory Committee (PBAC): http://www.pbs.gov.au/pbs/home
- Canadian Agency for Drugs and Technologies in Health (CADTH): https://www.cadth.ca/

- Haute Autorité de Santé (HAS): https://www.has-sante.fr
- Agenzia Nazionale per i Servizi Sanitari Regionali (AGENAS): https://www.agenas.gov.it/
- Ministry of Health, Labour and Welfare (MHLW): https://www.mhlw.go.jp/
- Agencia Española de Medicamentos y Productos Sanitarios (AEMPS): https://www.aemps.gob.es/

Further additionally searched databases were:

- CEA Registry: http://healtheconomics.tuftsmedicalcenter.org/cear2n/search/search.aspx
- EuroQol Group: www.euroqol.org
- The international HTA database of the International Network of Agencies for Health Technology Assessment: http://www.inahta.org/hta-database/

A manual search was performed on the reference lists of identified eligible studies and previously published relevant literature reviews.

Table 91 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	Embase.com	1974 to July 2024	08.07.2024
Medline	pubmed.ncbi.nlm.nih.gov	1946 to July 2024	08.07.2024
CENTRAL	Wiley platform	Inception to July 2024	08.07.2024
CDSR	Wiley platform	2020 to March 2021	30.03.2021
NHS EED	CRD interface	2021 to July 2024	08.07.2024
HTA	https://database.inahta.org/	2021 to July 2024	08.07.2024

Abbreviations: CDSR = Cochrane Database of Systematic Reviews; EED = Economic Evaluation Database; HTA = health technology assessment

Table 92 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
ClinicalTrials.gov	http://www.clinicaltrials.gov/	"Hepatitis d" OR "Hep d" OR "Hepatitis delta" OR "Delta virus" OR HDV	08.07.2024
International Clinical Trials Registry	https://www.who.int/ictrp/en/	"hepd" OR "Hepatitis AND delta" OR "hdv" OR "delta virus"	08.07.2024

Platform (ICTRP)			
EU Clinical Trials Register	https://www.clinicaltrialsregister.eu/	"Hepatitis d" OR "Hep d" OR "Hepatitis delta" OR "Delta virus" OR HDV	08.07.2024
PharmNet.Bund	https://www.pharmnet-bund.de/static/en/clinical-trials/index.html	"Hepatitis d" OR "Hep d" OR "Hepatitis delta" OR "Delta virus" OR HDV	08.07.2024
German Clinical Trials Register	https://www.bfarm.de/EN/BfArM/Tasks/German-Clinical-Trials-Register/	"Hepatitis d" OR "Hep d" OR "Hepatitis delta" OR "Delta virus" OR HDV	30.03.2021
International Standard Randomised Controlled Trial Number (ISRCTN) Registry	https://www.isrctn.com/	"Hepatitis d" OR "Hep d" OR "Hepatitis delta" OR "Delta virus" OR HDV	30.03.2021
National Institute for Health and Care Excellence (NICE)	http://www.nice.org.uk/	"Hepatitis d" OR "Hep d" OR "Hepatitis delta" OR "Delta virus" OR HDV	08.07.2024
Scottish Medicines Consortium (SMC)	http://scottishmedicines.org.uk	"Hepatitis d" OR "Hep d" OR "Hepatitis delta" OR "Delta virus" OR HDV	08.07.2024
All Wales Medicines Strategy Group (AWMSG)	https://www.gov.wales/all-wales-medicines-strategy-group	"Hepatitis d" OR "Hep d" OR "Hepatitis delta" OR "Delta virus" OR HDV	30.03.2021
German Institute for Quality and Efficiency in Health Care (IQWiG)	https://www.iqwig.de/	"Hepatitis d" OR "Hep d" OR "Hepatitis delta" OR "Delta virus" OR HDV	08.07.2024
Gemeinsamer Bundesausschuss (Federal Joint	https://www.g-ba.de/	"Hepatitis d" OR "Hep d" OR "Hepatitis delta" OR "Delta virus" OR HDV	08.07.2024

Committee, G-BA)			
Institute for Clinical and Economic Review (ICER)	https://icer-review.org/	"Hepatitis d" OR "Hep d" OR "Hepatitis delta" OR "Delta virus" OR HDV	08.07.2024
Pharmaceutical Benefits Advisory Committee (PBAC)	http://www.pbs.gov.au/pbs/home	"Hepatitis d" OR "Hep d" OR "Hepatitis delta" OR "Delta virus" OR HDV	08.07.2024
Canadian Agency for Drugs and Technologies in Health (CADTH)	https://www.cadth.ca/	"Hepatitis d" OR "Hep d" OR "Hepatitis delta" OR "Delta virus" OR HDV	08.07.2024
Haute Autorité de Santé (HAS)	https://www.has-sante.fr	"Hepatitis d" OR "Hep d" OR "Hepatitis delta" OR "Delta virus" OR HDV	08.07.2024
Agenzia Nazionale per i Servizi Sanitari Regionali (AGENAS)	https://www.agenas.gov.it/	N/A	30.03.2021
Ministry of Health, Labour and Welfare (MHLW)	https://www.mhlw.go.jp/	N/A	30.03.2021
Agencia Española de Medicamentos y Productos Sanitarios (AEMPS)	https://www.aemps.gob.es/	N/A	30.03.2021
CEA Registry	http://healtheconomics.tuftsmedicalcenter.org/cear2n/search/search.aspx	Hepatitis d	08.07.2024
EuroQol Group	https://www.euroqol.org/	Hepatitis d	08.07.2024

Abbreviations: N/A = not available

Table 93 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
American Association of Liver Diseases (AASLD)	conference website	Skimming through abstract collection	Hepatitis D HDV Delta virus Hep d Hepatitis delta	08.07.2024
European Association for the study of Liver Diseases (EASL)	conference website	Skimming through abstract collection	Hepatitis D HDV Delta virus Hep d Hepatitis delta	08.07.2024
International Liver Congress	conference website	Skimming through abstract collection	"Hepatitis d" OR "Hep d" OR "Hepatitis delta" OR "Delta virus" OR HDV	30.03.2021
European Congress for Clinical Microbiology and Infectious Diseases (ECCMID)	conference website	Skimming through abstract collection	Hepatitis D HDV Delta virus Hep d Hepatitis delta	08.07.2024
International Society for Pharmacoeconomics and Outcomes Research (ISPOR)	conference website	Skimming through abstract collection	"Hepatitis d" OR "Hep d" OR "Hepatitis delta" OR "Delta virus" OR HDV	08.07.2024
American Transplant Congress	conference website	Skimming through abstract collection	Hepatitis D HDV Delta virus Hep d Hepatitis delta	08.07.2024

American Society of Clinical Oncology (ASCO)	conference website	Skimming through abstract collection	N/A	30.03.2021
American Society of Hematology (ASH)	conference website	Skimming through abstract collection	N/A	30.03.2021

Abbreviations: N/A = not available

H.1.1 Search strategies

Table 76, Table 77, Table 78, and Table 79 present the search strategies for Embase, MEDLINE, CENTRAL, and NHS EED and HTA databases, performed on the 8th of July 2024 and capturing publications from January 2021.

Table 94 Search strategy for Embase and MEDLINE using Embase.com

No.	Query	Results
#1	'delta agent hepatitis'/exp	4180
#2	'hepatitis delta virus'/exp	4592
#3	'chronic hepatitis d'/exp	293
#4	'hepatitis d':ab,ti,kw,ok	2499
#5	'hepatitis delta':ab,ti,kw,ok	3002
#6	'hep d':ab,ti,kw,ok	11
#7	'hdv':ab,ti,kw,ok	4999
#8	'delta virus':ab,ti,kw,ok	2660
#9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8	9065
#10	'editorial'/exp OR 'letter'/exp	2024641
#11	'case report'/exp OR 'veterinary clinical trial'/exp	3095960
#12	#9 NOT (#10 OR #11)	8248
#13	(rat:ti OR rats:ti OR mouse:ti OR mice:ti OR swine:ti OR porcine:ti OR murine:ti OR sheep:ti OR lambs:ti OR pigs:ti OR piglets:ti OR rabbit:ti OR rabbits:ti OR cat:ti OR cats:ti OR dog:ti OR dogs:ti OR cattle:ti OR bovine:ti OR monkey:ti OR monkeys:ti OR trout:ti OR marmoset*:ti) AND 'animal experiment'/exp	1263390
#14	'animal experiment'/exp NOT ('human experiment'/exp OR 'human'/exp)	2654159

#15	#12 NOT (#13 OR #14)	8069
#16	#12 NOT (#13 OR #14) AND [01-12-2021]/sd NOT [09-07-2024]/sd	1499

Table 95 Search strategy for MEDLINE searched using PubMed platform

No.	Query	Results
#1	Search: Hepatitis D [MeSH] OR Hepatitis Delta Virus [MeSH] or "Hep D " [Title/Abstract] OR "hep d" [ot] OR "hepatitis D" [Title/Abstract] OR "hepatitis d" [ot] OR "hepatitis delta" [Title/Abstract] OR "hepatitis delta" [ot] OR HDV [Title/Abstract] OR HDV [ot] OR "delta virus" [Title/Abstract] OR "delta virus" [ot]	5,413
#2	Search: animals [mesh] NOT humans [mesh]	5,240,296
#3	Search: letter [pt] OR comment [pt] OR editorial [pt] OR news [pt]	2,469,554
#4	Search: case reports [mesh]	306
#5	Search: case reports [pt]	2,418,346
#6	Search: #1 NOT (#2 OR #3 OR #4 OR #5)	4,649
#7	#6 Filters: from 2022 - 2024	549
#8	#6 Filters: from 2023 - 2024	368

Table 96 Search strategy for CENTRAL searched using Cochrane Library

No.	Query	Results
#1	MeSH descriptor: [Hepatitis D] explode all trees	238
#2	MeSH descriptor: [Hepatitis Delta Virus] explode all trees	8
#3	("hep D"):ti,ab,kw	0
#4	("hepatitis d"):ti,ab,kw	166
#5	("hepatitis delta"):ti,ab,kw	126
#6	(hdv):ti,ab,kw	217
#7	"delta virus"	100
#8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7	515
#9	#8 in Trials	260

#10	#9 in the last 3 year	10

Table 97 Search strategy for NHS EED and HTA database searched using CRD University of York platform

No.	Query	Results
#1	MeSH DESCRIPTOR Hepatitis D EXPLODE ALL TREES	6
#2	((Hepatitis d) OR (hep d OR hdv) OR (hepatitis d or hepatitis delta or delta virus))	14
#3	#1 OR #2 [NHS EED and HTA database] 2021 to 2024	0

H.1.2 Systematic selection of studies

The research question contains elements that need to be defined before the start of the evidence collection. These include population, interventions, comparators, outcomes, and study design (PICOS) (Table 80).

Relevant studies were selected based on a two-step process: (1) title/abstract screening and (2) full-text screening.

Two investigators working independently screened all citations identified in the literature search. Similarly, two investigators independently reviewed the full texts. If any discrepancies occurred between the studies selected by the two investigators, a third investigator provided the arbitration. For data extraction, two investigators working independently extracted data on study characteristics, interventions, patient characteristics, and outcomes for the study population of interest for the final list of selected eligible studies. Any discrepancies observed between the data extracted by the two data extractors were resolved by discussion and coming to a consensus. Data were entered into a Microsoft Excel Workbook.

Table 98 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Population	Adult [aged ≥18 years] patients with chronic hepatitis delta who have compensated liver disease	• Patients without chronic hepatitis delta • Patients with chronic hepatitis delta who have decompensated liver disease • Patients <18 years old Mixed populations for which outcomes for adults with HDV are not presented separately	N/A

Intervention	• Hepcludex® (bulevirtide) • pegIFN-α • IFNα	Studies that do not investigate one of the interventions of interest in at least one of the arms	N/A
Comparators	• Nucleotide or nucleoside analogues • Placebo • Any included intervention	N/A	N/A
Outcomes	• HDV RNA undetectable • HDV RNA undetectable or reduced (>2 log) • HDV RNA response (undetectable) after 24 weeks follow-up • Combined response • ALT normalisation • HDV RNA change from baseline • ALT change from baseline • Adverse events	Studies that do not report data of interest	N/A
Study design/publication type	**Clinical Review** • Randomized, controlled, prospective clinical trials	**Clinical Review** • Preclinical studies or Phase 1 studies • Single-arm pilot trials • Prognostic studies • Cross-sectional studies • Prospective observational studies where the intervention is not determined by a protocol • Retrospective studies (e.g., case-control studies, historical-control studies) • Case reports, case series or case cohort studies • Consensus reports, Non-systematic reviews	N/A

Language restrictions	English language only[a]	Non-English language	N/A

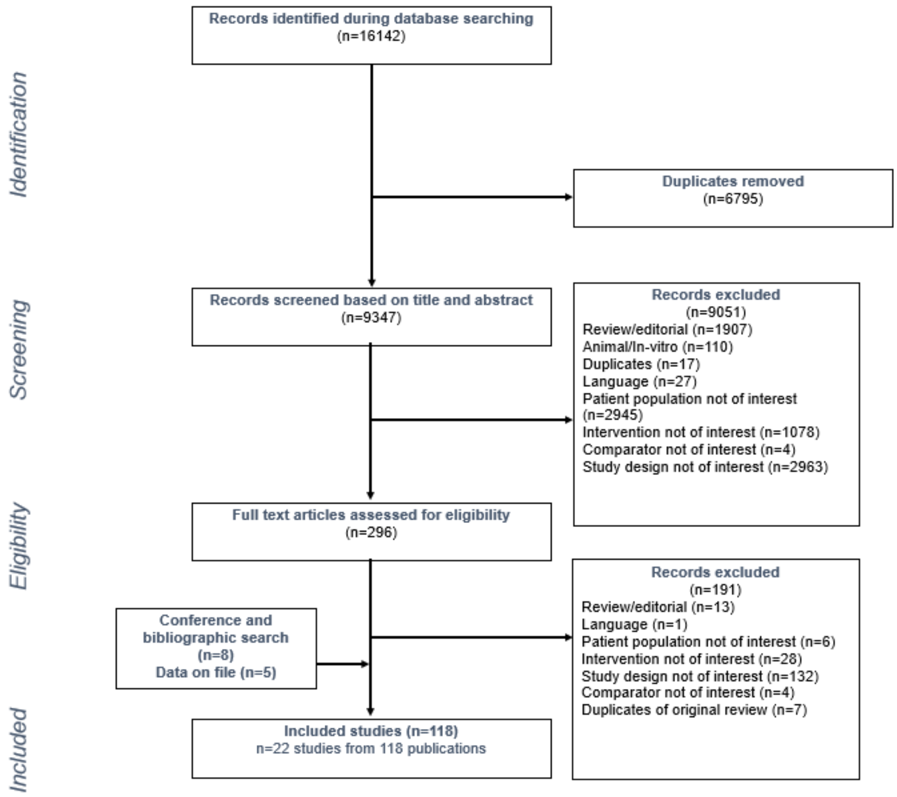
[a]English abstracts of non-English language studies were considered for inclusion.

Abbreviations: ALT = Alanine aminotransferase; HDV = hepatitis deltq virus; N/A = not applicable; pegIFN-α: Pegylated Interferon alpha

H.1.3 Results

As part of the July 2024 update, a total of 16,142 records were retrieved by the electronic database searches from database inception. Checking for the duplicates resulted in the exclusion of 6,795 hits, and the remaining 9,347 hits were screened. After preliminary screening of title/abstracts, 9,051 records were excluded, and 296 records were included for full publication screening. After a secondary screening of full-text articles, 191 studies were excluded. Additionally, eight studies were included from the bibliography and conference searching, and five studies (bulevirtide trials) were available as data on file. Ultimately, this resulted in the inclusion of 118 publications in the clinical SLR. Figure 24 presents the PRISMA flow diagram of studies identified in this review.

Figure 32 PRISMA flow for the clinical SLR from inception to 8th July 2024



Abbreviations: SLR = systematic literature review

Table 99 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
MYR301 NCT03852719	To evaluate the efficacy of bulevirtide administered subcutaneously for 48 weeks at a dose of 2 mg or 10 mg once daily for treatment of chronic hepatitis delta (CHD) in comparison to delayed treatment.	Multicenter, open-label, randomized Phase 3 clinical study of bulevirtide vs. delayed treatment/BSC	Treatment of adult patients with chronic hepatitis delta	Intervention: Bulevirtide 2 mg (N=49), bulevirtide 10 mg (N=50) Comparator: Delayed treatment/BSC (N=51)	The primary efficacy endpoint was the proportion of participants achieving combined response at Week 48, defined as the fulfillment of undetectable (< lower limit of quantitation, target not detected) HDV RNA or decreased by ≥ 2 log10 IU/mL from baseline and alanine aminotransferase (ALT) normalisation. After end of treatment (Week 144), patients entered a 96-weeks follow-up period.	• The proportion of participants with undetectable HDV RNA at Week 48 • The proportion of participants with ALT normalisation at Week 48 • The proportion of participants with undetectable HDV RNA 24 weeks after scheduled end of treatment (sustained virologic response at follow-up Week 24) • The proportion of participants with undetectable HDV RNA 48 weeks after scheduled end of treatment

(sustained virologic response at follow-up Week 48)

- Change from baseline in liver stiffness as measured by elastography at Weeks 48, 96, 144, 192, and 240
- The proportion of participants with HDV RNA decrease by ≥ 2 log10 IU/mL or undetectable HDV RNA at Week 48

After end of treatment (Week 144), patients entered a 96-weeks follow-up period.

Abbreviations: ALT = alanine aminotransferase; BSC = best supportive care; CHD = chronic hepatitis delta; HDV = hepatitis delta virus

A complete list of all included references is provided in Table 82.

Table 100 Complete list of included references in the clinical SLR

Title	Author	Year

Co-treatment with pegylated interferon alfa-2a and entecavir for hepatitis D: A randomized trial	Abbas, Z.; Memon, M. S.; Umer, M. A.; Abbas, M.; Shazi, L.	2016
Efficacy of interferon alpha-2b and lamivudine combination treatment in comparison to interferon alpha-2b alone in chronic delta hepatitis: a randomized trial	Canbakan, B.; Senturk, H.; Tabak, F.; Akdogan, M.; Tahan, V.; Mert, A.; Sut, N.; Ozaras, R.; Midilli, K.; Ozbay, G.	2006
Treatment of chronic hepatitis D with interferon alfa-2a	Farci, P.; Mandas, A.; Coiana, A.; Lai, M. E.; Desmet, V.; Van Eyken, P.; Gibo, Y.; Caruso, L.; Scaccabarozzi, S.; Criscuolo, D.; et al.	1994
Long-term follow-up after alfa-interferon treatment for chronic hepatitis D	Farci, P.; Chessa, L.; Peddis, G.; Orgiana, G.; Scioscia, R.; Degioannis, D.; Lai, E.; Mazzoleni, A. P.; Desmer, V.; Balestrieri, A.	1999
Long-term benefit of interferon alpha therapy of chronic hepatitis D: regression of advanced hepatic fibrosis	Farci, P.; Roskams, T.; Chessa, L.; Peddis, G.; Mazzoleni, A. P.; Scioscia, R.; Serra, G.; Lai, M. E.; Loy, M.; Caruso, L.; Desmet, V.; Purcell, R. H.; Balestrieri, A.	2004
Long-term outcome improvement in patients with chronic hepatitis D treated with interferon α	Ratziu, V.; Poynard, T.	2004
The French experience of treatment of chronic type D hepatitis with a 12-month course of interferon alpha-2B. Results of a randomized controlled trial	Gaudin, J. L.; Faure, P.; Godinot, H.; Gerard, F.; Trepo, C.	1995
Two-year interferon therapy with or without ribavirin in chronic delta hepatitis	Gunsar, F.; Akarca, U. S.; Ersoz, G.; Kobak, A. C.; Karasu, Z.; Yuce, G.; Ilter, T.; Batur, Y.	2005

Loss of HBsAg with interferon-alpha therapy in chronic hepatitis D virus infection	Lau, J. Y.; King, R.; Tibbs, C. J.; Catterall, A. P.; Smith, H. M.; Portmann, B. C.; Alexander, G. J.; Williams, R.	1993
Pegylated interferon alpha-2b as monotherapy or in combination with ribavirin in chronic hepatitis delta	Niro, G. A.; Ciancio, A.; Gaeta, G. B.; Smedile, A.; Marrone, A.; Olivero, A.; Stanzione, M.; David, E.; Brancaccio, G.; Fontana, R.; Perri, F.; Andriulli, A.; Rizzetto, M.	2006
A Study of Peginterferon Alfa-2a With or Without Ribavirin in Participants With Chronic Hepatitis D (CHD)	NCT02731131	2004
Treatment of chronic delta infection with recombinant human interferon alpha 2c at high doses	Porres, J. C.; Carreño, V.; Bartolomé, J.; Moreno, A.; Galiana, F.; Quiroga, J. A.	1989
Treatment of chronic delta hepatitis with α-2 recombinant interferon	Rizzetto, M.; Rosina, F.; Saracco, G.	1986
A randomized controlled trial of a 12-month course of recombinant human interferon-alpha in chronic delta (type D) hepatitis: a multicenter Italian study	Rosina, F.; Pintus, C.; Meschievitz, C.; Rizzetto, M.	1991
Long-term interferon therapy of chronic hepatitis D: a multicenter Italian study (Bologna, Cagliari, Genova, Milano, Napoli, Palermo, Pavia, Torino)	Rosina, F.; Pintus, C.	1989
Long term interferon treatment of chronic delta hepatitis: a multicenter Italian study	Rosina, F.; Pintus, C.; Meschievitz, C.; Rizzetto, M.	1991
Long-term interferon treatment of chronic hepatitis D: a multicentre Italian study	Rosina, F.; Pintus, C.; Rizzetto, M.	1990

Alpha 2 recombinant interferon in the treatment of chronic hepatitis delta virus (HDV) hepatitis	Rosina, F.; Saracco, G.; Lattore, V.; Quartarone, V.; Rizzetto, M.; Verme, G.; Trinchero, P.; Sansalvadore, F.; Smedile, A.	1987
Alpha interferon in the treatment of chronic delta hepatitis	Rosina, F.; Saracco, G.; Sansalvadore, F.; Giorda, L.; Actis, G.; Lattore, V.; Bonino, F.; Smedile, A.; Gerin, J. L.; Meschievitz, C.; Verme, G.; Rizzetto, M.	1989
MYR203, A multicentre, open-label, randomized, comparative, parallel-arm phase II study to assess efficacy and safety of Myrcludex B in combination with peginterferon alfa-2a versus peginterferon alfa-2a alone in patients with chronic viral hepatitis B with delta-agent.	MYR203	2019
Final results of a multicenter, open-label phase 2 clinical trial (MYR203) to assess safety and efficacy of myrcludex B in c with PEG-interferon Alpha 2a in patients with chronic HBV/HDV co-infection	Wedemeyer, H.; Schöneweis, K.; Bogomolov, P. O.; Voronkova, N.; Chulanov, V.; Stepanova, T.; Bremer, B.; Allweiss, L.; Dandri, M.; Burhenne, J.; Haefeli, W. E.; Ciesek, S.; Dittmer, U.; Alexandrov, A.; Urban, S.	2019
Safety and efficacy of 10 mg myrcludex B/IFNa combination therapy in patients with chronic HBV/HDV Co-infection	Wedemeyer, H.; Schöneweis, K.; Bogomolov, P.; Vorokova, N.; Chulanov, V.; Stepanova, T.; Allweiss, L.; Dandri, M.; Ciesek, S.; Dittmer, U.; Haefeli, W.; Alexandrov, A.; Urban, S.	2020
Safety and efficacy of 10mg (high-dose) bulevirtide (Myrcludex B) in combination with PEG-interferon alpha 2a or tenofovir in patients with chronic HBV/ HDV co-infection: Week 24 interim results of the MYR203 extension study	Wedemeyer, H.; Schöneweis, K.; Bogomolov, P.; Voronkova, N.; Chulanov, V.; Stepanova, T.; Allweiss, L.; Dandri, M.; Ciesek, S.; Haefeli, W. E.; Alexandrov, A.; Urban, S.	2019
48 weeks of high dose (10 mg) bulevirtide as monotherapy or with peginterferon alfa-2a in patients with chronic HBV/HDV co-infection	Wedemeyer, Heiner; Schöneweis, Katrin; Bogomolov, Pavel O.; Chulanov, Vladimir; Stepanova, Tatyana; Viacheslav, Morozov; Allweiss, Lena;	2020

	Dandri, Maura; Ciesek, Sandra; Dittmer, Ulf; Haefeli, Walter-Emil; Alexandrov, Alexander; Urban, Stephan	
Interim results of a multicentre, open-label phase 2 clinical trial (MYR203) to assess safety and efficacy of myrcludex B in combination with peg-interferon alpha 2a in patients with chronic HBV/HDV co-infection	Wedemeyer, H.; Schöneweis, K.; Bogomolov, P. O.; Voronkova, N. V.; Chulanov, V.; Stepanova, T.; Bremer, B.; Lehmann, P.; Raupach, R.; Alleiss, L.; Dandri, M.; Ciesek, S.; Dittmer, U.; Haefeli, W. E.; Alexandrov, A.; Urban, S.	2018
MYR202, A multicenter, open-label, randomized clinical study to assess efficacy and safety of 3 doses of Myrcludex B for 24 weeks in combination with Tenofovir compared to Tenofovir alone to suppress HBV replication in patients with chronic hepatitis D	MYR202	2019
Final results of a multicenter, open-label phase 2b clinical trial to assess safety and efficacy of Myrcludex B in combination with Tenofovir in patients with chronic HBV/HDV co-infection	Wedemeyer, H.; Bogomolov, P.; Blank, A.; Allweiss, L.; Dandri-Petersen, M.; Bremer, B.; Voronkova, N.; Schöneweis, K.; Pathil, A.; Burhenne, J.; Haag, M.; Schwab, M.; Haefeli, W. E.; Wiesch, J. S. Z.; Alexandrov, A.; Urban, S.	2018
Interim results of a multicenter, open-label phase 2b clinical trial to assess safety and efficacy of Myrcludex B in combination with Tenofovir in patients with chronic HBV/HDV co-infection	Wedemeyer, H.; Alexandrov, A.; Bogomolov, P.; Blank, A.; Bremer, B.; Voronkova, N.; Schoneweis, K.; Raupach, R.; Lehmann, P.; Darnedde, M.; Pathil, A.; Burhenne, J.; Haag, M.; Schwab, M.; Haefeli, W. E.; Urban, S.	2017
Strong intrahepatic decline of hepatitis D virus RNA and antigen after 24weeks of treatment with Myrcludex B in combination with Tenofovir in chronic HBV/HDV infected patients: Interim results from a multicenter, open-label phase 2b clinical trial	Allweiss, L.; Dettmer, C.; Volz, T.; Giersch, K.; Alexandrov, A.; Wedemeyer, H.; Urban, S.; Bockmann, J. H.; Luetgehmann, M.; Dandri, M.	2018

Analysis of liver biopsies reveals a strong intrahepatic reduction of HDV and inflammatory markers after treatment with Myrcludex b in combination with tenofovir in chronic HBV/HDV infected patients	Allweiss, L.; Volz, T. K.; Wedemeyer, H.; Schoneweis, K.; Alexandrov, A.; Bockmann, J. H.; Lohse, A. W.; Urban, S.; Lutgehetmann, M.; Dandri, M.	2019
A Multicenter, Open-label, Randomized Clinical Study to Assess Efficacy and Safety of 3 Doses of Myrcludex B for 24 Weeks in Combination With Tenofovir Compared to Tenofovir Alone to Suppress HBV Replication in Patients With Chronic Hepatitis D	NCT03546621	2016
Safety and efficacy of bulevirtide in combination with tenofovir disoproxil fumarate in patients with hepatitis B virus and hepatitis D virus coinfection (MYR202): a multicentre, randomised, parallel-group, open-label, phase 2 trial	Wedemeyer H., Schöneweis K., Bogomolov P., Blank A., Voronkova N., Stepanova T., Sagalova O., Chulanov V., Osipenko M., Morozov V., Geyvandova N., Sleptsova S., Bakulin I.G., Khaertynova I., Rusanova M., Pathil A., Merle U., Bremer B., Allweiss L., Lempp F.A., Port K., Haag M., Schwab M., zur Wiesch J.S., Cornberg M., Haefeli W.E., Dandri M., Alexandrov A., Urban S.	2023
Peginterferon plus adefovir versus either drug alone for hepatitis delta	Wedemeyer, H.; Yurdaydìn, C.; Dalekos, G. N.; Erhardt, A.; Çakaloğlu, Y.; Değertekin, H.; Gürel, S.; Zeuzem, S.; Zachou, K.; Bozkaya, H.; Koch, A.; Bock, T.; Dienes, H. P.; Manns, M. P.	2011
Long-term follow-up after peg-IFNa2a-based therapy of chronic hepatitis delta	Heidrich, B.; Yurdaydin, C.; Kabac¸am, G.; Zachou, K.; Bremer, B.; Dalekos, G. N.; Erhardt, A.; Cakaloɿlu, Y.; Yalcin, K.; Gürel, S.; Zeuzem, S.; Bock, T.; Idilman, R.; Manns, M. P.; Wedemeyer, H.	2013
Implications of hbsag, hbcag and hdag immunohistochemistry in course and treatment of chronic delta hepatitis (CDH)	Kabacam, G.; Wedemeyer, H.; Heidrich, B.; Yalcin, K.; Onder, F. O.; Dienes, H. P.; Manns, M. P.; Yurdaydin, C.	2012

Association Between Level of Hepatitis D Virus RNA at Week 24 of Pegylated Interferon Therapy and Outcome	Keskin, O.; Wedemeyer, H.; Tüzün, A.; Zachou, K.; Deda, X.; Dalekos, G. N.; Heidrich, B.; Pehlivan, S.; Zeuzem, S.; Yalçın, K.; Gürel, S.; Tabak, F.; Idilman, R.; Bozkaya, H.; Manns, M.; Yurdaydin, C.	2015
Reviving pegylated interferon as a therapeutic agent for hepatitis D: no more room for nucleos(t)ides?	Lutz, H. H.; Trautwein, C.	2011
Pegylated interferon-alfa-2a plus adefovir combination therapy is superior to pegylated interferon-alfa-2a alone or adefovir monotherapy in reducing HBsAG levels in HDV-coinfected patients with low HBV viremia	Wedemeyer, H.; Yurdaydin, C.; Zachou, K.; Erhardt, A.; Cakaloglu, Y.; Degertekin, H.; Gurel, S.; Zeuzem, S.; Dalekos, G.; Bock, T.; et al.	2007
Ten-year follow-up of a randomized controlled clinical trial in chronic hepatitis delta	Wranke, A.; Hardtke, S.; Heidrich, B.; Dalekos, G.; Yalçin, K.; Tabak, F.; Gürel, S.; Çakaloğlu, Y.; Akarca, U. S.; Lammert, F.; Häussinger, D.; Müller, T.; Wöbse, M.; Manns, M. P.; Idilman, R.; Cornberg, M.; Wedemeyer, H.; Yurdaydin, C.	2020
Efficacy of pegylated interferon-based treat-ent in patients with cirrhosis due to chronic delta hepatitis: Comparison with non-cirrhotic patients	Yurdaydin, C.; Kabacam, G.; Cakaloglu, Y.; Erhardt, A.; Degertekin, H.; Gurel, S.; Zeuzem, S.; Dalekos, G. N.; Bozkaya, H.; Dienes, H. P.; Manns, M. P.; Wedemeyer, H.	2009
72 week data of the HIDIT-1 trial: a multicenter randomised study comparing peginterferon alpha-2a plus adefovir vs. peginterferon alpha-2a plus placebo vs. adefovir in chronic delta hepatitis.	Wedermeyer, H; Yurdadin, C.; Dalekos, G.; Erhardt, A.; Cakaloglu, Y.; Degertekin, H.; et al	2007
Renal function during treatment with adefovir plus peginterferon alfa-2a vs either drug alone in hepatitis B/D co-infection	Mederacke I., Yurdaydin C., Großhennig A., Erhardt A., Cakaloglu Y., Yalcin K., Gurel S., Zeuzem S., Zachou K., Chatzikyrkou C., Bozkaya H., Dalekos G.N., Manns M.P., Wedemeyer H.	2012

A virological response to PEG-IFNa treatment of hepatitis delta is associated with an improved clinical long-term outcome: 10 years follow-up of the HIDIT-1 study	A. Wranke, C. Yurdaydin, B. Heidrich, Z. Kalliopi, K. Yalcin, T. Fehmi5, U. Akarca6, F. Lammert7, D. Häussinger8, T. Müller9, M. Wöbse1, M.P. Manns10, H. Wedemeyer11, S. Hardtke	2018
Peginterferon alfa-2a plus tenofovir disoproxil fumarate for hepatitis D (HIDIT-II): a randomised, placebo controlled, phase 2 trial	Wedemeyer, H.; Yurdaydin, C.; Hardtke, S.; Caruntu, F. A.; Curescu, M. G.; Yalcin, K.; Akarca, U. S.; Gürel, S.; Zeuzem, S.; Erhardt, A.; Lüth, S.; Papatheodoridis, G. V.; Keskin, O.; Port, K.; Radu, M.; Celen, M. K.; Idilman, R.; Weber, K.; Stift, J.; Wittkop, U.; Heidrich, B.; Mederacke, I.; von der Leyen, H.; Dienes, H. P.; Cornberg, M.; Koch, A.; Manns, M. P.	2019
96 weeks of pegylated-Interferon-alpha-2a plus tenofovir or placebo for the treatment of hepatitis delta: The HIDIT-2 study	Wedemeyer, H.; Yurdaydin, C.; Ernst, S.; Caruntu, F. A.; Curescu, M. G.; Yalcin, K.; Akarca, U. S.; Gurel, S.; Zeuzem, S.; Erhardt, A.; Lüth, S.; Papatheodoridis, G. V.; Keskin, O.; Port, K.; Celen, M. K.; Stift, J.; Heidrich, B.; Mederacke, I.; Hardtke, S.; Koch, A.; Dienes, H. P.; Manns, M. P.	2013
Prolonged therapy of hepatitis delta for 96 weeks with pegylated-interferon-a-2a plus tenofovir or placebo does not prevent HDVRNA relapse after treatment: the hidit-2 study	Wedemeyer, H.; Yurdaydin, C.; Ernst, S.; Caruntu, F. A.; Curescu, M. G.; Yalcin, K.; Akarca, U. S.; Gürel, S.; Zeuzem, S.; Erhardt, A.; Lüth, S.; Papatheodoridis, G. V.; Keskin, O.; Port, K.; Radu, M.; Celen, M. K.; Ildeman, R.; Stift, J.; Heidrich, B.; Mederacke, I.; Hardtke, S.; Koch, A.; Dienes, H. P.; Manns, M. P.	2014
On-treatment HBsAg kinetics to predict long-term HDVRNA response to peg-IFNa treatment of hepatitis delta	Wöbse, M.; Hardtke, S.; Ernst, S.; Benjamin, H.; Bremer, B.; Keskin, O.; Koch, A.; Manns, M. P.; Wedemeyer, H.; Yurdaydin, C.	2015
Early on-treatment HDV RNA kinetics are not predicitve for long-term response to a PEG-IFNa therapy of hepatitis delta	Wöbse, M.; Yurdaydin, C.; Ernst, S.; Hardtke, S.; Heidrich, B.; Bremer, B.; Keskin, O.; Idilman, R.; Koch, A.; Manns, M. P.; Wedemeyer, H.	2014

Pegylated-interferon-a-2a plus tenofovir or placebo for the treatment of hepatitis delta: First results of the HIDIT-2 study	Yurdaydin, C.; Wedemeyer, H.; Caruntu, F. A.; Curescu, M. G.; Yalcin, K.; Akarca, U. S.; Gurel, S.; Zeuzem, S.; Erhardt, A.; Lüth, S.; Papatheodoridis, G. V.; Port, K.; Keskin, O.; Radu, M. N.; Celen, M. K.; Idilman, R.; Stift, J.; Mederacke, I.; Heidrich, B.; Manns, M. P.; Dienes, H. P.	2012
Residual low HDV viremia is associated with HDV RNA relapse after PEG-IFNa-based antiviral treatment of hepatitis D (delta): results from the HIDIT-II study	Bremer, Birgit; Anastasiou, Olympia; Hardtke, Svenja; Caruntu, Florin Alexandru; Curescu, Manuela Gabriela; Yalcin, Kendal; Akarca, Ulus S.; Gurel, Selim; Idilman, Ramazan; Zeuzem, Stefan; Erhardt, Andreas; Lüth, Stefan; Papatheodoridis, George; Radu, Monica; Manns, Michael P.; Cornberg, Markus; Yurdaydin, Cihan; Wedemeyer, Heiner	2020
Frequency, severity and impact of Peg-IFNa-associated flares in HDV infection: Results from the HIDIT-II study	Hardtke, S.; Wedemeyer, H.; Caruntu, F. A.; Curescu, M.; Kendal, Y.; Akarca, U.; Yurdcu, E.; Gurel, S.; Zeuzem, S.; Erhardt, A.; Lüth, S.; Papatheodoridis, G.; Keskin, O.; Port, K.; Radu, M.; Tabak, F.; Idilman, R.; Bozdayi, M.; Koch, A.; Manns, M. P.; Cornberg, M.; Yurdaydin, C.	2019
HBcrAg Levels Are Associated With Virological Response to Treatment With Interferon in Patients With Hepatitis Delta	Sandmann L., Yurdaydin C., Deterding K., Heidrich B., Hardtke S., Lehmann P., Bremer B., Manns M.P., Cornberg M., Wedemeyer H., Maasoumy B.	2022
Five-year follow-up of 96 weeks peginterferon plus tenofovir disoproxil fumarate in hepatitis D	Anastasiou O.E., Caruntu F.A., Curescu M.G., Yalcin K., Akarca U.S., Gürel S., Zeuzem S., Erhardt A., Lüth S., Papatheodoridis G.V., Keskin O., Port K., Radu M., Celen M.K., Idilman R., Heidrich B., Mederacke I., von der Leyen H., Kahlhöfer J., von Karpowitz M., Hardtke S., Cornberg M., Yurdaydin C., Wedemeyer H.	2024
Five years follow-up of 96 weeks peginterferon plus tenofovir disoproxil fumarate in hepatitis D	Anastasiou O.A., Caruntu F.A., Curescu M.G., Yalcin K., Akarca U.S., Gurel S., Zeuzem S., Erhardt A., Lüth S., Papatheodoridis G., Keskin O., Port K., Radu M., Celen M., Idilman R., Heidrich B., Mederacke I., von der Leyen	2023

	H., Kahlhöfer J., von Karpowitz M., Hardtke S., Cornberg M., Yurdaydin C., Wedemeyer H.	
HBV RNA levels are associated with virological response to treatment with pegylated interferon alpha in patients with chronic hepatitis D virus infection	Sandmann L., Bremer B., Yurdaydin C., Deterding K., Manns M.P., Cornberg M., Wedemeyer H., Maasoumy B.	2022
Treatment of chronic delta hepatitis with lamivudine vs lamivudine + interferon vs interferon	Yurdaydin, C.; Bozkaya, H.; Onder, F. O.; Sentürk, H.; Karaaslan, H.; Akdoğan, M.; Cetinkaya, H.; Erden, E.; Erkan-Esin, O.; Yalçin, K.; Bozdayi, A. M.; Schinazi, R. F.; Gerin, J. L.; Uzunalimoğlu, O.; Ozden, A.	2008
Treatment of chronic hepatitis D (CHD) with interferon vs. interferon + lamivudine vs. lamivudine: short-and long-term results	Yurdaydin, C.; Bozkaya, H.; Onder, O.; Senturk, H.; Fried, M.; Idilman, R.	2005
Randomized open-label substudy of daily Myrcludex B plus pegylated interferon-alpha-2a in patients with HBeAg negative chronic hepatitis B co-infected with hepatitis delta	MYR201	2017
Treatment of chronic hepatitis D with the entry inhibitor myrcludex B: First results of a phase Ib/IIa study	Bogomolov P., Alexandrov A., Voronkova N., Macievich M., Kokina K., Petrachenkova M., Lehr T., Lempp F.A., Wedemeyer H., Haag M., Schwab M., Haefeli W.E., Blank A., Urban S.	2016
A proof-of-concept Phase IIa clinical trial to treat chronic HBV/HDV with the entry inhibitor myrcludex B	Bogomolov P., Voronkova N., Schoeneweis K., Schwab M., Lempp F.A., Haag M., Wedemeyer H., Alexandrov A., Haefeli W.E., Blank A., Urban S.	2016
Myrcludex B Plus Pegylated Interferon-alpha-2a in Patients With HBeAg Negative HBV/HDV Co-infection	NCT02637999	2014

MYR204, Phase 2b Study of Bulevirtide (With Peginterferon Alfa-2a) in Patients With CHD	MYR204	2021
Safety and efficacy of bulevirtide monotherapy and in combination with peginterferon alfa-2a in patients with chronic hepatitis delta: 24 weeks interim data of MYR204 phase 2b study	Asselah T., Arama S.S., Bogomolov P., Bourliere M., Fontaine H., Gherlan G.S., Gorodin V., Hilleret M.-N., Lazar S., Mamonova N., Viacheslav M., Pantea V., Placinta G., Gournay J., Raffi F., Ratziu V., Stern C., Sagalova O., Samuel D., Stepanova T., Syutkin V., Suri V., Manuilov D., Flaherty J.F., Streinu-Cercel A., Zoulim F., Roulot D.	2022
Efficacy and safety of bulevirtide in combination with pegylated interferon alfa-2a in patients with chronic hepatitis delta: primary endpoint results from a phase 2b open-label, randomized, multicenter study MYR204	Asselah T., Lampertico P., Wedemeyer H., Streinu-Cercel A., Pantea V., Lazar S., Placinta G., Gherlan G.S., Bogomolov P., Stepanova T., Morozov V., Chulanov V., Syutkin V.E., Sagalova O., Gorodin V., Manuilov D., Mercier R.-C., Ye L., Flaherty J.F., Osinusi A.O., Lau A.H., Da B.L., Bourliere M., Ratziu V., Pol S., Hilleret M.-N., Zoulim F.	2024
Bulevirtide Combined with Pegylated Interferon for Chronic Hepatitis D	Asselah T., Chulanov V., Lampertico P., Wedemeyer H., Streinu-Cercel A., Pântea V., Lazar S., Placinta G., Gherlan G.S., Bogomolov P., Stepanova T., Morozov V., Syutkin V., Sagalova O., Manuilov D., Mercier R.-C., Ye L., Da B.L., Chee G., Lau A.H., Osinusi A., Bourliere M., Ratziu V., Pol S., Hilleret M.-N., Zoulim F.	2024
Bulevirtide as monotherapy for chronic hepatitis d infection: week 48 results from integrated efficacy and safety analyses	Aleman S., Lampertico P., Asselah T., Manuilov D., Suri V., Ye L., Flaherty J., Cornberg M., Brunetto M., Wedemeyer H.	2023
SAT-371 No amino acid substitution in HBV PreS1, HDAg, or NTCP associated with suboptimal response to bulevirtide in combination with pegylated interferon alfa-2a treatment in participants with chronic hepatitis delta: results from MYR204 a phase 2b study	Yang Liu,Silvia Chang,Simin Xu,...Fabien Zoulim,Evguenia Maiorova,Hongmei Mo Published in issue: June 2024	2024

WED-395 Undetectable hepatitis delta virus RNA at the end of treatment with bulevirtide and pegylated interferon alpha-2a is an important predictor of 48 weeks sustained virologic response in chronic hepatitis delta	Fabien Zoulim,Tarik Asselah,Vladimir Chulanov,...Marc Bourliere,Heiner Wedemeyer,Pietro Lampertico	2024
Safety and efficacy of bulevirtide monotherapy and in combination with Peginterferon alfa-2a in patients with chronic hepatitis delta: 24 weeks interim data of MYR204 Phase 2b study	Tarik Asselah, Sorin Stefan Arama, Pavel Bogomolov, Marc Bourliere, Hélè ne Fontaine, George Sebastian Gherlan,Vladimir Gorodin, Marie-Noëlle Hilleret, Stefan Lazar,	2021
MYR301, Phase 3 Study of Bulevirtide in Patients With CHD	MYR301	2021
Bulevirtide monotherapy in patients with chronic HDV: Efficacy and safety results through week 96 from a phase 3 randomized trial	Wedemeyer H., Aleman S., Brunetto M., Blank A., Andreone P., Bogomolov P., Chulanov V., Mamonova N., Geyvandova N., Morozov V., Sagalova O., Stepanova T., Berger A., Ciesek S., Manuilov D., Mercier R.-C., Da B.L., Chee G.M., Li M., Flaherty J.F., Lau A.H., Osinusi A., Schulze Zur Wiesch J., Cornberg M., Zeuzem S., Lampertico P.	2024
Efficacy and Safety of Bulevirtide Monotherapy Given at 2-mg or 10-mg Dose Level Once Daily for Treatment of Chronic Hepatitis Delta: Week 48 Primary Endpoint Results from a Phase 3 Randomized, Multicenter, Parallel-Design Study	Wedemeyer H., Aleman S., Brunetto M., Blank A., Andreone P., Bogomolov P., Morozov V., Manuilov D., Suri V., An Q., Flaherty J.F., Zur Wiesch J.S., Cornberg M., Zeuzem S., Lampertico P.	2022
A Phase 3, Randomized Trial of Bulevirtide in Chronic Hepatitis D	Wedemeyer H., Aleman S., Brunetto M.R., Blank A., Andreone P., Bogomolov P., Chulanov V., Mamonova N., Geyvandova N., Morozov V., Sagalova O., Stepanova T., Berger A., Manuilov D., Suri V., An Q., Da B., Flaherty J., Osinusi A., Liu Y., Merle U., Schulze Zur Wiesch J., Zeuzem S., Ciesek S., Cornberg M., Lampertico P.	2023

Efficacy and safety at 96 weeks of bulevirtide 2 mg or 10 mg monotherapy for chronic hepatitis delta: results from an interim analysis of a phase 3 randomized study	Wedemeyer H., Aleman S., Brunetto M., Blank A., Andreone P., Bogomolov P., Chulanov V., Mamonova N., Geyvandova N., Morozov V., Sagalova O., Stepanova T., Manuilov D., Mercier R.-C., An Q., Flaherty J., Osinusi A., Lau A., Wiesch J.S.Z., Cornberg M., Zeuzem S., Lampertico P.	2023
Efficacy and safety of bulevirtide monotherapy given at 2-mg or 10-mg dose level once daily for treatment of chronic hepatitis delta: Week 48 primary endpoint results from a Phase 3 randomized, multicenter, parallel design study	Wedemeyer H., Deterding K., Aleman S., Brunetto M., Blank A., Andreone P., Bogomolov P., Chulanov F.V., Mamonova N., Geyvandova N., Morozov V., Sagalova O., Stepanova T., Manuilov D., Suri V., An Q., Flaherty J., Schulze Zur Wiesch J., Osinusi A., Cornberg M., Zeuzem S., Lampertico P.	2023
Efficacy and safety at 96 weeks of bulevirtide 2 mg or 10 mg monotherapy for chronic hepatitis delta: results from an interim analysis of a phase 3 randomized study	Wedemeyer H., Aleman S., Brunetto M.R., Blank A., Andreone P., Bogomolov P., Chulanov V., Mamonova N., Geyvandova N., Morozov V., Sagalova O., Stepanova T.V., Manuilov D., Mercier R.-C., An Q., Flaherty J.F., Osinusi A., Lau A.H., Wiesch J.S.Z., Cornberg M., Zeuzem S., Lampertico P.	2024
Efficacy and safety of bulevirtide monotherapy given at 2 mg or 10 mg dose level once daily for treatment of chronic hepatitis delta: week 48 primary end point results from a phase 3 randomized, multicenter, parallel design study	Wedemeyer H., Aleman S., Brunetto M., Blank A., Andreone P., Bogomolov P., Chulanov V., Mamonova N., Geyvandova N., Viacheslav M., Sagalova O., Stepanova T., Manuilov D., Suri V., An Q., Flaherty J.F., Osinusi A., zur Wiesch J.S., Cornberg M., Zeuzem S., Lampertico P.	2022
Efficacy and safety at 96 weeks of bulevirtide 2 mg or 10 mg monotherapy for chronic hepatitis D: results from an interim analysis of a phase 3 randomized study	Wedemeyer H., Aleman S., Brunetto M., Blank A., Andreone P., Bogomolov P., Chulanov V., Mamonova N., Geyvandova N., Viacheslav M., Sagalova O., Stepanova T., Manuilov D., Mercier R.-C., An Q., Flaherty J.F., Osinusi A., Lau A., Wiesch J.S.Z., Cornberg M., Zeuzem S., Lampertico P.	2023

Efficacy and Safety of Bulevirtide Monotherapy Given at 2 mg or 10 mg Dose Level Once Daily for Treatment of Chronic Hepatitis Delta: Week 48 Primary Endpoint Results from a Phase 3 Randomized, Multicenter, Parallel Design Study	Heiner W., Soo A., Maurizia B., Antje B., Pietro A., Pavel B., Vladimir C., Nina M., Natalia G., Viacheslav M., Olga S., Tatyana S., Dmitry M., Vithika S., Qi A., John F., Anu O., Schulze Z.W.J., Markus C., Stefan Z., Pietro L.	2023
Bulevirtide monotherapy at low and high dose in patients with chronic hepatitis delta: 24 weeks interim data of the phase 3 MYR301 study	Wedemeyer H., Aleman S., Andreone P., Blank A., Brunetto M., Bogomolov P., Chulanov V., Geyvandova N., Hilgard G., Mamonova N., Merle U., Viacheslav M., Sagalova O., Stepanova T., Zur Wiesch J.S., Zotov S., Suri V., Manuilov D., Flaherty J.F., Zeuzem S., Lampertico P.	2022
Bulevirtide monotherapy at low and high dose in patients with chronic hepatitis delta: 24 weeks interim data of the phase 3 MYR301 study	Wedemeyer H., Aleman S., Andreone P., Blank A., Brunetto M., Bogomolov P., Chulanov V., Geyvandova N., Hilgard G., Mamonova N., Merle U., Viacheslav M., Sagalova O., Stepanova T., zur Wiesch J.S., Zotov S., Zeuzem S., Lampertico P.	2022
Continued treatment of early non-responder or partial virologic responders with bulevirtide monotherapy in patients with chronic hepatitis D through week 96 leads to improvement in virologic and biochemical responses	Lampertico P., Wedemeyer H., Brunetto M., Bogomolov P., Stepanova T., Ciesek S., Berger A., Manuilov D., An Q., Lau A., Da B., Flaherty J.F., Mercier R.-C., Zeuzem S., Cornberg M., Buti M., Aleman S.	2023
Continued Treatment of Early Nonresponders or Partial Virologic Responders with Bulevirtide Monotherapy in Patients With Chronic Hepatitis Delta Through Week 96 Leads to Improvement in Virologic and Biochemical Responses	Lampertico P., Wedemeyer H., Brunetto M.R., Bogomolov P., Stepanova T., Ciesek S., Berger A., Manuilov D., An Q., Lau A., Da B., Flaherty J., Mercier R.-C., Zeuzem S., Cornberg M., Buti M., Aleman S.	2023
Bulevirtide monotherapy at low and high doses in patients with chronic hepatitis delta: 24-week interim data of the Phase 3 MYR301 study	Freismuth A., Wedemeyer H., Aleman S., Brunetto M., Black A., Andreone P., Bogomolov P., Chulanov V., Mamonova N., Geyvandova N., Morozov	2022

	V., Sagalova O., Stepanova T., Manuilov D., Suri V., An Q.I., Flaherty J.F., Osinusi A., Schulze Zur Wiesch J., Cornberg M., Zeuzem S., Lampertico P.	
HIGH RATES OF ADHERENCE TO BULEVIRTIDE MONOTHERAPY FOR CHRONIC HEPATITIS DELTA THROUGH 96 WEEKS: RESULTS FROM AN INTERIM ANALYSIS OF THE PHASE 3 STUDY MYR301	Aleman S., Wedemeyer H., Brunetto M.R., Blank A., Andreone P., Bogomolov P., Chulanov V., Mamonova N., Geyvandova N., Morozov V., Sagalova O., Stepanova T.V., Da B., Manuilov D., Chee G., Li M., Lau A.H., Wiesch J.S.Z., Cornberg M., Zeuzem S., Lampertico P.	2024
Bulevirtide Monotherapy at Low and High Dose in Patients With Chronic Hepatitis Delta: 24-Week Interim Data of the Phase 3 MYR301 Study	Lee S., Wedemeyer H., Aleman S., Brunetto M., Blank A., Andreone P., Bogomolov P., Chulanov V., Mamonova N., Geyvandova N., Morozov V., Sagalova O., Stepanova T., Manuilov D., Suri V., An Q., Flaherty J.F., Osinusi A., Zur Wiesch J.S., Cornberg M., Zeuzem S., Lampertico P.	2022
Continued treatment of early nonresponder or partial virologic responders with bulevirtide monotherapy in patients with chronic hepatitis delta (CHD) through week 96 leads to improvement in virologic and biochemical responses	Lampertico P., Wedemeyer H., Brunetto M., Bogomolov P., Stepanova T., Ciesek S., Berger A., Manuilov D., An Q., Lau A., Da B., Flaherty J., Mercier R.-C., Zeuzem S., Cornberg M., Buti M., Aleman S.	2023
No detectable resistance to bulevirtide monotherapy through 96 weeks treatment in patient with chronic hepatitis D	Aleman S., Liu Y., Xu S., Chang S., Martin R., Aeschbacher T., May L., Manhas S., Han D., Yazdi T., Martinez C., Ho P.Y., Richards C., Marceau C., Manuilov D., Flaherty J.F., Maiorova E., Mo H., Wedemeyer H., Lampertico P.	2023
Continued treatment of early virologic nonresponder or partial responders with bulevirtide monotherapy for chronic hepatitis D leads to improvement in virologic and biochemical responses: results from an integrated analysis at week 96	Lampertico P., Wedemeyer H., Brunetto M.R., Bogomolov P., Bourliere M., Fontaine H., Chee G., Manuilov D., An Q., Lau A.H., Da B.L., Flaherty J.F., Mercier R.-C., Frenette C., Osinusi A.O., Gherlan G.S., Zeuzem S., Cornberg M., Roulot D.M., Zoulim F., Aleman S., Asselah T.	2023

Integrated efficacy analysis of 24-week data from two phase 2 and one phase 3 clinical trials of bulevirtide monotherapy given at 2 mg or 10 mg dose level for treatment of chronic hepatitis delta	Lampertico P., Aleman S., Blank A., Bogomolov P., Chulanov V., Mamonova N., Viacheslav M., Sagalova O., Stepanova T., Suri V., Manuilov D., Ye L., Flaherty J.F., Osinusi A., Cornberg M., Brunetto M., Wedemeyer H.	2022
Integrated Safety Analysis of 24-Week Data from Three Phase 2 and One Phase 3 Clinical Trials of Bulevirtide Monotherapy Given at 2 mg and 10 mg Dose Level for Treatment of Chronic Hepatitis Delta	Lampertico P., Aleman S., Asselah T., Bourliere M., Streinu-Cercel A., Bogomolov P., Morozov V., Stepanova T., Lazar S., Suri V., Manuilov D., Ye L., Flaherty J.F., Brunetto M., Wedemeyer H.	2022
Integrated safety analysis of 24-week data from three phase 2 and one phase 3 clinical trials of bulevirtide monotherapy given at 2 mg and 10 mg dose level for treatment of chronic hepatitis delta	Lampertico P., Aleman S., Asselah T., Bourliere M., Streinu-Cercel A., Bogomolov P., Viacheslav M., Stepanova T., Lazar S., Suri V., Manuilov D., Ye L., Flaherty J.F., Osinusi A., Brunetto M., Wedemeyer H.	2022
Strong decline of intrahepatic HDV markers and signs of liver infammation after 48 weeks of treatment with Bulevirtide in chronic hepatitis D patients: Combined intrahepatic results from the clinical trials MYR203 and MYR301	Lena A., Annika V., Yvonne L., Corinna E., Vithika S., Jefrey W., John F., Dmitry M., Marc L.-M., Heiner W., Stephan U., Jan-Hendrik B., Maura D.	2023
Efficacy of bulevirtide as monotherapy for chronic hepatitis D (CHD): Week 48 results from an integrated analysis	Lampertico P., Aleman S., Blank A., Bogomolov P., Chulanov V., Mamonova N., Morozov V., Sagalova O., Stepanova T., Suri V., Manuilov D., Ye L., Flaherty J.F., Osinusi A., Cornberg M., Brunetto M., Wedemeyer H.	2023
Efficacy of bulevirtide as monotherapy for chronic hepatitis D (CHD): Week 48 results from an integrated analysis	Lampertico P., Aleman S., Blank A., Bogomolov P., Chulanov V., Mamonova N., Morozov V., Sagalova O., Stepanova T., Suri V., Manuilov D., Ye L., Flaherty J.F., Osinusi A.O., Cornberg M., Brunetto M., Wedemeyer H.	2022

Bulevirtide Monotherapy Is Safe and Well Tolerated in Patients With Chronic Hepatitis D (CHD): An Integrated Safety Analysis of 48-Week Data	Asselah T., Lampertico P., Aleman S., Bourliere M., Streinu-Cercel A., Bogomolov P., Morozov V., Stepanova T., Lazar S., Suri V., Manuilov D., Mercier R.-C., Tseng S., Ye L., Flaherty J.F., Osinusi A.O., Brunetto M., Wedemeyer H.	2022
Relationship of hepatitis D viral load, ALT levels, and liver stiffness in untreated patients with chronic hepatitis D	Aleman S., Lampertico P., Brunetto M., Bogomolov P., Chulanov V., Mamonova N., Stepanova T., Manuilov D., An Q., Da B., Flaherty J.F., Mercier R.-C., Lau A., Zeuzem S., Cornberg M., Wedemeyer H.	2023
Integrated Efficacy Analysis of 24-Week Data from Two Phase 2 and One Phase 3 Clinical Trials of Bulevirtide Monotherapy Given at 2 mg or 10 mg Dose Levels for Treatment of Chronic Hepatitis Delta	Lampertico P., Aleman S., Blank A., Bogomolov P., Chulanov V., Mamonova N., Morozov V., Stepanova T., Suri V., Manuilov D., Ye L., Flaherty J.F., Cornberg M., Brunetto M., Wedemeyer H.	2022
Blocking viral entry with bulevirtide reduces the number of HDV-infected hepatocytes in human liver biopsies	Allweiss L., Volmari A., Suri V., Wallin J.J., Flaherty J.F., Manuilov D., Downie B., Lütgehetmann M., Bockmann J.-H., Urban S., Wedemeyer H., Dandri M.	2024
Development of Antidrug Antibodies on Bulevirtide Monotherapy in Chronic Hepatitis Delta does not impact Bulevirtide Efficacy, Safety, or Pharmacokinetics	Lampertico P., Aleman S., Bogomolov P., Morozov V., Mamonova N., Manuilov D., Ye L., Da B.L., Mercier R.-C., Lau A.H., Chee G., Mallalieu N., Kumar P., Stepanova T., Chulanov V., Zeuzem S., Wedemeyer H., Bourliere M., Zoulim F., Asselah T., Brunetto M.R., Cornberg M., Blank A.	2023
Bulevirtide monotherapy is safe and well tolerated in patients with chronic hepatitis D (CHD): An integrated safety analysis of 48-week data	Asselah T., Lampertico P., Aleman S., Bourliere M., Streinu-Cercel A., Bogomolov P., Morozov V., Stepanova T., Lazar S., Suri V., Manuilov D., Mercier R.C., Tseng S., Ye L., Flaherty J.F., Osinusi A., Brunetto M., Wedemeyer H.	2023

Improvement in Noninvasive Markers of Fibrosis (LSM, FIB-4, and APRI) is seen over 96 Weeks of Bulevirtide Monotherapy in Chronic Hepatitis Delta regardless of Virologic Response	Castera L., Aleman S., Lampertico P., Bogomolov P., Manuilov D., An Q., Da B.L., Flaherty J.F., Mercier R.-C., Lau A.H., Chee G., Stepanova T., Zeuzem S., Wedemeyer H., Bourliere M., Zoulim F., Asselah T., Brunetto M.R.	2023
Treatment with bulevirtide (BLV) for 48 weeks reduces necroinflammation: results from a histological subset analysis of patients enrolled in studies MYR203 and MYR301	Flaherty J., Lampertico P., Aleman S., Brunetto M., Guo Y., Frenette C., Cornberg M., Bogomolov P., Wedemeyer H., Suri V.	2023
No detectable resistance to bulevirtide in participants with chronic hepatitis D (CHD) through 24 weeks of treatment	Hollnberger J., Liu Y., Martin R., Manhas S., Aeschbacher T., Chang S., Xu S., Han B., Yazdi T., May L., Han D., Schöneweis K., Flaherty J.F., Suri V., Manuilov D., Mateo R., Svarovskaia E.S., Mo H., Urban S.	2022
SAT-373 Intrahepatic sodium taurocholate co-transporting polypeptide gene transcript and membrane-localized protein expression changes in chronic hepatitis D patients following 48 weeks of treatment with Bulevirtide	Wildaliz Nieves,David Pan,Abhishek Aggarwal,...Renee-Claude Mercier,Jeffrey Wallin,Maura Dandri-Petersen	2024
TOP-400 Impact of bulevirtide given with or without nucleos (t)ide analogues on 48-week virologic outcomes in patients with chronic hepatitis delta virus infection	Pietro Lampertico,Maurizia Brunetto,Maria Buti,...Markus Cornberg,Heiner Wedemeyer,Tarik Asselah	2024
Strong intrahepatic decline of hepatitis d virus rna and antigen after 48 weeks of treatment with bulevirtide in chronic hbv/hdv co-infected patients: Interim results from a multicenter, open-label, randomized phase 3 clinical trial (myr301)	Allweiss L., Volmari A., Ladiges Y., Eggers C., Giersch K., Schöneweis K., Suri V., Wallin J., Wedemeyer H., Urban S., Lütgehetmann M., Bockmann J.-H., Dandri M.	2021

Treatment with bulevirtide improves patient reported outcomes in patients with chronic hepatitis delta (chd): An interim exploratory analysis at week 24	Wedemeyer H., Aleman S., Chulanov V., Hilgard G., Antonova J., Kaushik A.M., Lloyd A., Manuilov D., Suri V., Tran T.T., Osinusi A.O., Lampertico P., Morozov V., Sagalova O., Stepanova T., Buti M.	2021
Bulevirtide monotherapy at low and high dose in patients with chronic hepatitis delta: 24 weeks interim data of the phase 3 MYR301 study	Heiner Wedemeyer, Soo Aleman, Pietro Andreone, Antje Blank, Maurizia Brunetto, Pavel Bogomolov, Vladimir Chulano, Natalia Geyvandova, Gudrun Hilgard	2021
Week 48 results of the phase 3 D-LIVR study, a randomized double-blind, placebo-controlled trial evaluating the safety and efficacy of Lonafarnib-boosted with Ritonavir with or without Peginterferon Alfa in patients with chronic hepatitis delta	Etzion O., Hamid S.S., Asselah T., Gherlan G.S., Turcanu A., Petrivna T., Weissfeld L., Choong I., Hislop C., Apelian D., Buti M., Gheorghe L., Iliescu E.L., Voronkova N., Barsukova N., Aleman S., Feld J.J., Reau N.S., Brunetto M., Lampertico P., Heller T., Koh C., Yurdaydin C., Glenn J.	2023
Characterization of HDV RNA kinetic patterns during treatment: The D-LIVR Phase 3 study CHARACTERIZATION OF HDV RNA KINETIC PATTERNS DURING TREATMENT: THE D-LIVR PHASE 3 STUDY	Hershkovich L., Dahari H., Cotler S.J., Choong I., Hislop C., Dahari O., Heller T., Koh C., Glenn J., Asselah T., Hamid S.S., Etzion O.	2024
Clinical features predictive of cirrhosis in a large cohort of patients with chronic hepatitis delta infection- Insights from the D-LIVR trial	Etzion O., Buti M., Yardeni D., Nevo-Shor A., Munteanu D., Choong I., Weissfeld L., Abu-Freha N., Howard R., Asselah T., Lampertico P.	2022
Strong correlation between HBsAg, ALT and HDV-RNA levels in patients with chronic hepatitis D. Results of phase 3 D-LIVR study.	Buti M., Etzion O., Palom A., Yardeni D., Nevo-Shor A., Munteanu D., Choong I., Weissfeld L., Barciela M.R., Abu-Freha N., Barreira A., Howard R., Asselah T., Lampertico P.	2022
Limited utility of noninvasive tests for prediction of biopsy-proven cirrhosis in chronic hepatitis D infected patients-insights from the D-LIVR trial	Etzion O., Buti M., Yardeni D., Palom A., Nevo-Shor A., Munteanu D., Choong I., Wagstaff J., Riveiro-Barciela M., Abufreha N., Marchand C.C., Howard R., Barreira-Diaz A., Novack V., Asselah T.	2021

Treatment of chronic hepatitis D with peginterferon lambda - the phase 2 LIMT-1 clinical trial	Etzion O., Hamid S., Lurie Y., Gane E.J., Yardeni D., Duehren S., Bader N., Nevo-Shor A., Channa S.M., Cotler S.J., Mawani M., Parkash O., Dahari H., Choong I., Glenn J.S.	2023
Phase 3 Study to Evaluate the Efficacy and Safety of Peginterferon Lambda for 48 Weeks in Patients With Chronic HDV (LIMT-2)		2021

Abbreviations: SLR = systematic literature review

H.1.4 Excluded fulltext references

Table 101 List of excluded references in the clinical SLR (December 2021 SLR update)

Title	Author	Year	Reason for exclusion
A Phase 2, Open-Label Study of the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamic Activity of Titrating-Dose Lonafarnib in Combination with Ritonavir in Patients Chronically Infected with Hepatitis Delta Virus (LOWR-4)	-	-	Intervention
A Multicenter, Open-label, Randomized Phase 3 Clinical Study to Assess Efficacy and Safety of Bulevirtide in Patients with Chronic Hepatitis Delta	-	-	Study design
A multicenter randomised study comparing the efficacy of pegylated interferon-alfa-2a plus placebo vs. pegylated interfeorn-alfa-2a plus tenofovir for the treatment of chronic delta hepatitis- The Hep-Net International Delta hepatits Interventional Trial II (HIDIT-II)	-	-	Study design
A Phase 3, Matrix Design, Partially Double-Blind, Randomized Study of the Efficacy and Safety of 50 mg Lonafarnib/100 mg Ritonavir BID with and			Study design

without 180 mcg PEG IFN-alfa-2a for 48 Weeks Compared with PEG IFN-alfa-2a Monotherapy and Placebo Treatment in Patients Chronically Infected with Hepatitis Delta Virus Being Maintained on Anti-HBV Nucleos(t)ide Therapy (D-LIVR)			
Interferon alpha versus any other drug for chronic hepatitis D	Abbas, Z.; Ali, S. S.; Shazi, L.	2015	Review
Interferon-alpha for Hepatitis D: A systematic review	Abbas, Z.; Khan, A.; Salih, M.; Jafri, W.	2010	Review
Interferon alpha for chronic hepatitis D	Abbas, Z.; Khan, M. A.; Salih, M.; Jafri, W.	2011	Review
Treatment of chronic hepatitis D patients with pegylated interferon	Abbas, Z.; Memon, M. S.; Mithani, H.; Hamid, S. S.; Jafri, W.	2013	Study design
Treatment of chronic hepatitis D patients with pegylated interferon: a real-world experience	Abbas, Z.; Memon, M. S.; Mithani, H.; Jafri, W.; Hamid, S.	2014	Study design
An experience of pegylated interferon in patients with chronic hepatitis D	Abbas, Z.; Mithani, H.; Raza, S.	2011	Study design
Interferon lambda-3 polymorphism and response to pegylated interferon in patients with hepatitis D	Abbas, Z.; Yakoob, J.; Umer, M. A.; Abbas, M.; Hamid, S.	2015	Study design
Treatment of chronic hepatitis B with interferon-alpha: cost-effectiveness in developing countries	Aggarwal, R.; Ghoshal, U. C.; Naik, S. R.	2002	Patient population not of interest

Comparison the effectiveness of 72-and 96-week courses of antiviral therapy with pegylated interferon in the treatment of chronic hepatitis D	Aghayeva, G.; Hidayatov, A.	2017	Study design
Standard and pegylated interferon therapy of HDV infection: A systematic review and meta- analysis	Alavian, S. M.; Tabatabaei, S. V.; Behnava, B.; Rizzetto, M.	2012	Review
The diagnostic value of liver cirrhosis with different etiologies in hepatocelullar carcinoma	Anton, C.; Hârtie, C.; Plescufa, R.; Bistriceanu, S.; Dimache, M.; Anton, S.; Negru, D.	2017	Intervention
Efficiency of pegylated interferon alpha as monotherapy in chronic hepatitis delta infection	Bahcecioglu, I. H.; Aygun, C.; Gozel, N.; Bulut, Y.	2010	Study design
Pegylated Interferon α Therapy in Chronic Delta Hepatitis: A One-Center Experience	Bahcecioglu, I. H.; Ispiroglu, M.; Demirel, U.; Yalniz, M.	2015	Study design
Elimination of hepatitis delta virus infection after loss of hepatitis B surface antigen in patients with chronic delta hepatitis	Battegay, M.; Simpson, L. H.; Hoofnagle, J. H.; Sallie, R.; Di Bisceglie, A. M.	1994	Study design
Update on the safety and efficacy of rep 2139 monotherapy and subsequent combination therapy with pegylated interferon alpha-2a in chronic HBV/HDV Co-infection in Caucasian patients	Bazinet, M.; Pantea, V.; Cebotarescu, V.; Cojuhari, L.; Jimbei, P.; Albrecht, J.; Schmid, P.; Karimzadeh, H.; Roggendorf, M.; Vaillant, A.	2015	Study design
Initial follow up results from the REP 301 trial: Safety and efficacy of REP 2139-Ca and pegylated	Bazinet, M.; Pantea, V.; Cebotarescu, V.; Cojuhari, L.; Jimbei, P.; Albrecht, J.; Schmid,	2016	Study design

interferon alpha-2a in caucasian patients with chronic HBV / HDV Co-infection	P.; Krawczyk, A.; Karimzadeh, H.; Roggendorf, M.; Vaillant, A.		
Update on the safety and efficacy of REP 2139 monotherapy and subsequent combination therapy with pegylated interferon alpha-2a in caucasian patients with chronic HBV/HDV co-infection	Bazinet, M.; Pantea, V.; Cebotarescu, V.; Cojuhari, L.; Jimbei, P.; Albrecht, J.; Schmid, P.; Krawczyk, A.; Karimzadeh, H.; Roggendorf, M.; Vaillant, A.	2016	Study design
Safety and efficacy of REP 2139 and pegylated interferon alfa-2a for treatment-naive patients with chronic hepatitis B virus and hepatitis D virus co-infection (REP 301 and REP 301-LTF): a non-randomised, open-label, phase 2 trial	Bazinet, M.; Pântea, V.; Cebotarescu, V.; Cojuhari, L.; Jimbei, P.; Albrecht, J.; Schmid, P.; Le Gal, F.; Gordien, E.; Krawczyk, A.; Mijočević, H.; Karimzadeh, H.; Roggendorf, M.; Vaillant, A.	2017	Study design
Ongoing analysis of functional control / cure of HBV and HDV infection following rep 2139-CA and pegylated interferon alpha-2a therapy in patients with chronic HBV / HDV co-infection: 3-year followup results from the rep 301-ltf study	Bazinet, M.; Pântea, V.; Cebotarescu, V.; Cojuhari, L.; Jimbei, P.; Krawczyk, A.; Dittmer, U.; Vaillant, A.	2019	Study design
One year follow-up and HBV RNA / HBcrAg analysis in the REP 301 Trial: REP 2139 and pegylated interferon alpha-2a in Caucasian patients with chronic HBV / HDV co-infection	Bazinet, M.; Pantea, V.; Cebotarescu, V.; Cojuhari, L.; Jimbei, P.; Krawczyk, A.; Vaillant, A.	2017	Study design
REP 2139 monotherapy and combination therapy with pegylated interferon: Safety and potent	Bazinet, M.; Pantea, V.; Cebotarescu, V.; Cojuhari, L.; Jimbei, P.; Vaillant, A.	2015	Study design

reduction of HBsAg and HDV RNA in Caucasian Patients with chronic HBV/HDV co-infection			
Significant reduction of HBsAg and HDVRNA by the nucleic acid polymer rep 2139 in caucasian patients with chronic HBV/HDV co-infection	Bazinet, M.; Pantea, V.; Cebotarescu, V.; Cojuhari, L.; Jimbei, P.; Vaillant, A.	2015	Study design
Update on safety and efficacy in the REP 401 protocol: REP 2139- Mgor REP 2165-Mg used in combination with tenofovir disoproxil fumarate and pegylated Interferon alpha-2a in treatment naïve caucasian patients with chronic HBeAg negative HBV infection	Bazinet, M.; Pantea, V.; Placinta, G.; Moscalu, I.; Cebotarescu, V.; Cojuhari, L.; Jimbei, P.; Iarovoi, L.; Smesnoi, V.; Musteata, T.; et al.	2017	Review
Evaluation of the safety and tolerability of transaminase flares during antiviral therapy in patients with HBeAg negative chronic HBV infection or HBV/HDV co-infection	Bazinet, M.; Pantea, V.; Placinta, G.; Moscalu, I.; Cebotarescu, V.; Cojuhari, L.; Jimbei, P.; Iarovoi, L.; Smesnoi, V.; Musteata, T.; Jucov, A.; Krawczyk, A.; Vaillant, A.	2019	Study design
HBV-infection in Germany-costs in a real-life setting	Becker, H.; Stahmeyer, J. T.; Orlemann, A. L.; Krauth, C.; Manns, M.; Wedemeyer, H.	2016	Study design
Impact of Tenofovir on Hepatitis Delta Virus Replication in the Swiss Human Immunodeficiency Virus Cohort Study	Béguelin, C.; Friolet, N.; Moradpour, D.; Sahli, R.; Suter-Riniker, F.; Lüthi, A.; Cavassini, M.; Günthard, H. F.; Battegay, M.; Bernasconi, E.; Schmid, P.; Calmy, A.; Atkinson, A.; Rauch, A.; Wandeler, G.	2017	Intervention

Antiretroviral therapy and hepatitis delta replication in HIV-coinfected patients	Béguelin, C.; Moradpour, D.; Sahli, R.; Günthard, H. F.; Battegay, M.; Calmy, A. L.; Bernasconi, E.; Rauch, A.; Wandeler, G.	2016	Intervention
A proof-of-concept Phase IIa clinical trial to treat chronic HBV/HDV with the entry inhibitor myrcludex B	Bogomolov, P.; Voronkova, N.; Schoeneweis, K.; Schwab, M.; Lempp, F. A.; Haag, M.; Wedemeyer, H.; Alexandrov, A.; Haefeli, W. E.; Blank, A.; Urban, S.	2016	Study design
Treatment of hepatitis delta virus genotype 3 infection with peg-interferon and entecavir	Borzacov, L. M.; de Figueiredo Nicolete, L. D.; Souza, L. F.; Dos Santos, A. O.; Vieira, D. S.; Salcedo, J. M.	2016	Study design
Effect of tenofovir with and without interferon on hepatitis D virus replication in HIV-hepatitis B virus-hepatitis D virus-infected patients	Boyd, A.; Miailhes, P.; Brichler, S.; Scholtès, C.; Maylin, S.; Delaugerre, C.; Chevallier-Queyron, P.; Gordien, E.; Girard, P. M.; Lacombe, K.	2013	Study design
Patients with HDV infection and advanced fibrosis/cirrhosis present a high but predictable risk of developing hepatocellular carcinoma	Brancaccio, G.; Grossi, A.; Fasano, M.; Santantonio, T. A.; Gaeta, G. B.	2016	Intervention
Role of lamivudine in the posttransplant prophylaxis of chronic hepatitis B virus and hepatitis delta virus coinfection	Caccamo, L.; Agnelli, F.; Reggiani, P.; Maggi, U.; Donato, M. F.; Gatti, S.; Paone, G.; Melada, E.; Rossi, G.	2007	Study design

Hepatitis B core-related antigen (HBCRAG) is useful marker in HBV/HDV co-infection and can help to predict response to pegylated interferon therapy	Carey, I.; Bruce, M.; Montague, S.; Spaan, M.; Byrne, R.; Childs, K.; Wang, B.; Dusheiko, G. M.; Agarwal, K.	2017	Study design
Efficacy of peginterferon alpha-2b in chronic hepatitis delta: relevance of quantitative RT-PCR for follow-up	Castelnau, C.; Le Gal, F.; Ripault, M. P.; Gordien, E.; Martinot-Peignoux, M.; Boyer, N.; Pham, B. N.; Maylin, S.; Bedossa, P.; Dény, P.; Marcellin, P.; Gault, E.	2006	Study design
Application of Traditional Chinese Medicine in prevention and treatment of chronic viral hepatitis	Chi, Ctr Trc	2010	Intervention
Nucleos(T)ide analogue prophylaxis after hepatitis B immunoglobulin withdrawal is safe and effective against hepatitis B and D recurrence after liver transplantation	Cholongitas, E.; Vasiliadis, T.; Goulis, I.; Antoniadis, N.; Chalevas, P.; Fouzas, I.; Giakoustidis, D.; Imvrios, G.; Giouleme, O.; Papanikolaou, V.; Akriviadis, E.	2015	Intervention
Depression scores of delta hepatitis patients treated with pegylated interferon alfa	Dagli, O.; Mutlu, E. A.	2018	Study design
Polymerase chain reaction-based detection of hepatitis D virus genome in patients infected with human immunodeficiency virus	Dény, P.; Lecot, C.; Jeantils, V.; Ovaguimian, L.; Krivitzky, A.; Bréchot, C.	1993	Intervention
The long-term course of chronic hepatitis B	Di Marco, V.; Lo Iacono, O.; Cammà, C.; Vaccaro, A.; Giunta, M.; Martorana, G.; Fuschi, P.; Almasio, P. L.; Craxì, A.	1999	Study design

Pharmacokinetics and pharmacodynamics modeling of ritonavir boosted lonafarnib therapy in HDV patients: a phase 2 LOWRHDV- 3 study	Dubey, P.; Koh, C.; Surana, P.; Uprichard, S.; Han, M. A. T.; Fryzek, N.; Subramanya, G.; Kapuria, D.; Etzion, O.; Takyar, V.; et al.	2018	Intervention
Disease and economic burdens of hepatitis delta in The United States	Elsaid, M.; Narayanan, N.; Li, Y.; Rustgi, V. K.	2018	Study design
Economic and Health Care Burdens of Hepatitis Delta: A Study of Commercially Insured Adults in the United States	Elsaid, M. I.; Li, Y.; John, T.; Narayanan, N.; Catalano, C.; Rustgi, V. K.	2020	Study design
Healthcare cost and utilization in hepatitis delta: Analysis of privately insured patients in The United States	Elsaid, M. I.; Li, Y.; Ram Pentakota, S.; John, T.; Catalano, C.; Rustgi, V. K.	2019	Study design
Treatment of chronic hepatitis delta with pegylated interferon-alpha2b	Erhardt, A.; Gerlich, W.; Starke, C.; Wend, U.; Donner, A.; Sagir, A.; Heintges, T.; Häussinger, D.	2006	Study design
Characterization of HDV, HBsAg and ALT kinetics under peginterferon-lambda monotherapy: The phase 2 lint study	Etzion, O.; Duehren, S.; Hamid, S. S.; Lurie, Y.; Gane, E. J.; Yardeni, D.; Nevo-Shor, A.; Channa, S.; Parkash, O.; Uprichard, S. L.; Gish, R. G.; Cotter, S. J.; Glenn, J.; Apelian, D.; Dahari, H.; Mawani, M.	2019	Comparator
End of study results from LIMT HDV study: 36% durable virologic response at 24 weeks post-treatment with pegylated interferon lambda	Etzion, O.; Hamid, S. S.; Lurie, Y.; Gane, E.; Bader, N.; Yardeni, D.; Nevo-Shor, A.; Channa, S.; Mawani, M.; Parkash, O.; Yang,	2019	Comparator

monotherapy in patients with chronic hepatitis delta virus infection	K.; Longo, D.; Gish, R. G.; Glenn, J.; Apelian, D.		
This study will use an investigational product (bulevirtide) for the treatment of chronic hepatitis Delta to learn the therapeutic effect, and safety of the drug in humans	Euctr, F. R.	2019	Study design
Efficacy and Safety of bulevirtide in patients with Chronic Hepatitis Delta	Euctr, S. E.	2019	Study design
Treatment of delta hepatitis with pegylated interferon-alfa-2a and tenofovir or placebo	EUCTR2008-005560-13-DE	2009	Study design
Efficacy of antiviral therapy in 102 Romanian patients with chronic hepatitis delta	Gheorghe, L.; Iacob, S.; Simionov, I.; Vadan, R.; Constantinescu, I.	2012	Study design
Weight-based dosing regimen of peg-interferon α-2b for chronic hepatitis delta: a multicenter Romanian trial	Gheorghe, L.; Iacob, S.; Simionov, I.; Vadan, R.; Constantinescu, I.; Caruntu, F.; Sporea, I.; Grigorescu, M.	2011	Study design
Efficacy of pegylated interferon alpha-2B in a Romanian cohort with chronic hepatitis delta	Gheorghe, L.; Iacob, S.; Simionov, I.; Vadan, R.; Constantinescu, I.; Sporea, I.; Grigorescu, M.	2011	Study design
Pegylated interferon alpha-2B for the management of patients with chronic hepatitis delta	Gheorghe, L.; Iacob, S.; Simionov, I. I.; Vadan, R.; Constantinescu, I.; Sporea, I.; Grigorescu, M. D.	2011	Study design

Outcomes of response guided therapy with pegylated interferon alpha 2a in chronic hepatitis B and D	Gherlan, G. S.; Lazar, S.; Culinescu, A.; Daniela, S.; Cazan, A. R.; Popescu, C. P.; Paunescu, A.; Filip, L.; Florescu, S.; Calistru, P.; Ceausu, E.	2019	Study design
Quantification of HDV RNA Level in HDV seropositive patients	Gidaagaya, S.; Barsuren, B.; Batmunkh, M.; Namdag, B.	2018	Intervention
Spontaneous fluctuations of HDV RNA in the natural course of chronic hepatitis delta: Implications for the definition of therapy response	Godoy, C.; Sopena, S.; Tabernero, D.; Barciela, M. R.; Cortese, M. F.; Casillas, R.; Rando, A.; Vila, M.; Yll, M.; Esteban, R.; Buti, M.; Rodríguez-Frías, F.	2018	Study design
Recognizing the impact of endemic hepatitis D virus on hepatitis B virus eradication	Goyal, A.; Murray, J. M.	2016	Study design
Cost-Effectiveness of Peg-Interferon, Interferon and Oral Nucleoside Analogues in the Treatment of Chronic Hepatitis B and D Infections in China	Goyal, A.; Murray, J. M.	2016	Study design
Screening for hepatitis D and PEG-Interferon over Tenofovir enhance general hepatitis control efforts in Brazil	Goyal, A.; Romero-Severson, E. O.	2018	Study design
Overview of research on health-related quality of life in patients with chronic liver disease	Gutteling, J. J.; de Man, R. A.; Busschbach, J. J.; Darlington, A. S.	2007	Review

A phase 2 randomized clinical trial to evaluate the safety and efficacy of pegylated interferon lambda monotherapy in patients with chronic hepatitis delta virus infection. interim results from the limt HDV study	Hamid, S. S.; Etzion, O.; Lurie, Y.; Bader, N.; Yardeni, D.; Channa, S. M.; Mawani, M.; Parkash, O.; Martins, E. B.; Gane, E. J.	2017	Comparator
Treatment patterns, health care use, and costs associated with first-line treatment for chronic hepatitis B with oral antivirals recommended by current guidelines versus oral antivirals not recommended by current guidelines	Han, S. B.; Jing, W.; Mena, E. A.; Li, M.; Pinsky, B.; Tang, H.; Hebden, T.; Juday, T.	2011	Patient population not of interest
Long-term, high-dose peginterferon alfa-2a is an effective treatment for Chronic hepatitis D	Heller, T.; Rotman, Y.; Haynes-Williams, V.; Kleiner, D. E.; Ghany, M. G.; Liang, T. J.; Hoofnagle, J. H.	2009	Study design
Long-term therapy of chronic delta hepatitis with peginterferon alfa	Heller, T.; Rotman, Y.; Koh, C.; Clark, S.; Haynes-Williams, V.; Chang, R.; McBurney, R.; Schmid, P.; Albrecht, J.; Kleiner, D. E.; Ghany, M. G.; Liang, T. J.; Hoofnagle, J. H.	2014	Study design
Hepatitis DELTA virus RNA level and IgM antibody titer predict response to peg-interferon therapy	Hughes, S.; Carey, I.; Shang, D.; Bruce, M. J.; Horner, M.; Fletcher, I.; Cross, T. J.; Agarwal, K.; Harrison, P. M.	2009	Study design
Resistance of hepatitis delta virus replication to interferon-alpha treatment in transfected human cells	Ilan, Y.; Klein, A.; Taylor, J.; Tur-Kaspa, R.	1992	Study design

Differential hepatitis B virus (HBV) and hepatitis D virus (HDV) specific T cell response in HDV RNA positive and negative patients	Joshi, S.; Sadler, M.; Borman, M.; Israelson, H.; Smith, A.; Swain, M.; Coffin, C. S.	2020	Intervention
Interferon treatment of delta hepatitis: the longer the duration the better the success?	Kabacam, G.; Yakut, M.; Seven, G.; Bozkaya, H.; Idilman, R.; Yurdaydin, C.	2011	Study design
Delta hepatitis may require prolonged treatment with interferon	Kabacam, G.; Yakut, M.; Seven, G.; Karatayli, S. C.; Nassiri, C.; Bozkaya, H.; Bozdayi, A. M.; Idilman, R.; Yurdaydin, C.	2011	Study design
Efficacy of pegylated interferon-α treatment for 24 months in chronic delta hepatitis and predictors of response	Karaca, C.; Soyer, O. M.; Baran, B.; Ormeci, A. C.; Gokturk, S.; Aydin, E.; Evirgen, S.; Akyuz, F.; Demir, K.; Besisik, F.; Kaymakoglu, S.	2013	Study design
IL28B polymorphisms and influence on sustained virological response to interferon therapy in chronic delta hepatitis	Karaca, C.; Yilmaz, E.; Soyer, O. M.; Onel, D.; Onel, M.; Baran, B.; Ormeci, A.; Gokturk, S.; Evirgen, S.; Akyuz, F.; Demir, K.; Besisik, F.; Kaymakoglu, S.	2013	Study design
Alpha interferon and ribavirin combination therapy of chronic hepatitis D	Kaymakoglu, S.; Karaca, C.; Demir, K.; Poturoglu, S.; Danalioglu, A.; Badur, S.; Bozaci, M.; Besisik, F.; Cakaloglu, Y.; Okten, A.	2005	Study design
Two years therapy of chronic hepatitis delta with pegylated interferon-alpha-2a	Kemal Celen, M.; Ayaz, C.; Bayan, K.; Dal, T.; Altindis, M.	2015	Study design

Interferon alpha-2b therapy in chronic hepatitis delta	Keshvari, M.; Alavian, S. M.; Sharafi, H.; Karimi, G.; Gholami Fesharaki, M.	2014	Study design
TEN-YEAR FOLLOW-UP OF LONG-TERM PEGINTERFERONALPHA TREATMENT FOR CHRONIC DELTA HEPATITIS	Kim, Grace E; Hercun, J.; Da, Ben; Kleiner, D E; Chang, Richard; Koh, C.; Heller, Theo	2020	Study design
Oral prenylation inhibition with lonafarnib in chronic hepatitis D infection: A randomized, double-blinded, placebo-controlled proof-of-concept study	Koh, C.; Canini, L.; Dahari, H.; Cory, D.; Choong, I.; Kleiner, D.; Cooper, S.; Winters, M. A.; Glenn, J.; Heller, T.	2015	Intervention
Oral prenylation inhibition with lonafarnib in chronic hepatitis D infection: a proof-of-concept randomised, double-blind, placebo-controlled phase 2A trial	Koh, C.; Canini, L.; Dahari, H.; Zhao, X.; Uprichard, S. L.; Haynes-Williams, V.; Winters, M. A.; Subramanya, G.; Cooper, S. L.; Pinto, P.; Wolff, E. F.; Bishop, R.; Ai Thanda Han, M.; Cotler, S. J.; Kleiner, D. E.; Keskin, O.; Idilman, R.; Yurdaydin, C.; Glenn, J. S.; Heller, T.	2015	Intervention
A Phase 2 Study of Peginterferon Lambda, Lonafarnib and Ritonavir for 24 Weeks: End-of-Treatment Results from the LIFT HDV Study	Koh, Christopher; Hercun, Julian; Rahman, Farial; Huang, Amy; Da, Ben; Surana, Pallavi; Kapuria, Devika; Rotman, Yaron; Vittal, Anusha; Gilman, Christy Ann; Yakov, Gil Ben; Lai, Walter; Dahari, Harel; Glenn, Jeffrey; Heller, Theo	2020	Study design
A phase 2 study exploring once daily dosing of ritonavir boosted lonafarnib for the treatment of	Koh, C.; Surana, P.; Han, T.; Fryzek, N.; Kapuria, D.; Etzion, O.; Takyar, V.; Rotman,	2017	Intervention

chronic delta hepatitis - End of study results from the LOWR HDV-3 study	Y.; Canales, R.; Dahari, H.; Yurdaydin, C.; Glenn, J.; Heller, T.		
Prenylation inhibition with lonafarnib decreases hepatitis D levels in humans	Koh, C.; Yurdaydin, C.; Cooper, S.; Cory, D.; Dahari, H.; Haynes-Williams, V.; Winters, M. A.; Bys, M.; Choong, I. C.; Idilman, R.; Keskin, O.; Canini, L.; Pinto, P.; Wolff, E. F.; Bishop, R.; Kleiner, D. E.; Hoofnagle, J. H.; Glenn, J.; Heller, T.	2014	Intervention
High dose interferon alpha is the best therapeutic option for hepatitis delta; A systematic analysis of randomized controlled trials	Lamers, M.; Özenturk, Ö; Heidrich, B.; Wedemeyer, H.; Drenth, J. P.	2011	Review
Interferon-α for patients with chronic hepatitis delta: a systematic review of randomized clinical trials	Lamers, M. H.; Kirgiz, ÖÖ; Heidrich, B.; Wedemeyer, H.; Drenth, J. P.	2012	Review
Health-state utilities in liver disease: a systematic review	McLernon, D. J.; Dillon, J.; Donnan, P. T.	2008	Review
Pegylated Interferon to Treat Chronic Hepatitis D	NCT00023322	2001	Study design
Efficacy of Peginterferon Alfa-2b in Previously Untreated Subjects With Chronic Hepatitis B and D Co-infection (Study P04603)	NCT00686790	2005	Study design
Lonafarnib for Chronic Hepatitis D	NCT01495585	2011	Intervention

Treatment of Chronic Delta Hepatitis With Lonafarnib and Ritonavir	NCT02511431	2015	Intervention
A Study of Pegylated Interferon (PEG-IFN) Alfa-2a (Pegasys) in Participants With Chronic Hepatitis D (CHD)	NCT02732639	2005	Study design
A Phase 2b Study of Lonafarnib With or Without Ritonavir in Patients With HDV	NCT02960360	2017	Intervention
Study of the Efficacy and Safety of Lonafarnib Ritonavir With and Without Pegylated Interferon - Alfa-2a	NCT03719313	2018	Study design
Lamivudine therapy in chronic delta hepatitis: a multicentre randomized-controlled pilot study	Niro, G. A.; Ciancio, A.; Tillman, H. L.; Lagget, M.; Olivero, A.; Perri, F.; Fontana, R.; Little, N.; Campbell, F.; Smedile, A.; Manns, M. P.; Andriulli, A.; Rizzetto, M.	2005	Intervention
HBsAg kinetics in chronic hepatitis D during interferon therapy: on-treatment prediction of response	Niro, G. A.; Smedile, A.; Fontana, R.; Olivero, A.; Ciancio, A.; Valvano, M. R.; Pittaluga, F.; Coppola, N.; Wedemeyer, H.; Zachou, K.; Marrone, A.; Fasano, M.; Lotti, G.; Andreone, P.; Iacobellis, A.; Andriulli, A.; Rizzetto, M.	2016	Study design
Basal values and on treatment decline of hepatitis B core-related antigen are predictive of response to interferon therapy in chronic hepatitis D	Olivero, A.; Caviglia, G. P.; Ciancio, A.; Bosco, C.; Fontana, R.; Niro, G.; Rizzetto, M.; Maria Saracco, G.; Smedile, A.	2018	Study design

Short- and long-term effects of treatment of chronic hepatitis B and delta virus by IFN	Ormeci, N.	2003	Review
Adaptation and Calibration of a Markov MODEL Framework in Hepatitis D	Ouared, C; Massetti, M; Brandt, A S; Kozaris, T; Leleu, H.	2020	Study design
The composition of HBsAg during peginterferon-alfa2a treatment can predict treatment response in HBV/HDV-coinfection	Pfefferkorn, Maria; Luise, Drechsel; Rother, Karen; Santisteve, Sara Sopena; Renate, Heyne; Buti, Maria; Lampertico, Pietro; Glebe, Dieter; Berg, Thomas; van Bömmel, Florian	2020	Study design
Treatment of chronic hepatitis D with interferon alpha-2b in patients with human immunodeficiency virus infection	Puoti, M.; Rossi, S.; Forleo, M. A.; Zaltron, S.; Spinetti, A.; Putzolu, V.; Rodella, A.; Carosi, G.	1998	Study design
Treatment of HBV and HDV co-infection using lamivudine	Qureshi, H.; Arif, A.; Alam, E.	2009	Study design
Treatment of chronic type D (delta) hepatitis with alpha interferon	Rosina, F.; Rizzetto, M.	1989	Review
Italian trials of interferon alpha in chronic delta hepatitis	Rosina, F.; Saracco, G.; Cozzolongo, R.; Costa, C.; Bonino, F.; Verme, G.; Rizzetto, M.	1993	Review
Successful management of precarious population after systematic HBV testing in france: A prospective cohort study	Roudot-Thoraval, F.; Rosa-Hézode, I.; Trompette, M.; Costes, L.; Chousterman, M.	2015	Study design

Treatment of chronic hepatitis delta virus with peg-interferon and factors that predict sustained viral response	Samiullah, S.; Bikharam, D.; Nasreen	2012	Study design
Autoantibodies and response to α-interferon in patients with chronic viral hepatitis	Saracco, G.; Touscoz, A.; Durazzo, M.; Rosina, F.; Donegani, E.; Chiandussi, L.; Gallo, V.; Petrino, R.; De Micheli, A. G.; Solinas, A.; Deplano, A.; Tocco, A.; Cossu, P. A.; Pintus, C.; Verme, G.; Rizzetto, M.	1990	Study design
Comparing the performance of the standard EQ-5D 3L with the new version EQ-5D 5L in patients with chronic hepatic diseases	Scalone, L.; Ciampichini, R.; Fagiuoli, S.; Gardini, I.; Fusco, F.; Gaeta, L.; Del Prete, A.; Cesana, G.; Mantovani, L. G.	2013	Patient population not of interest
Treatment of chronic hepatitis delta virus with peg-interferon and factors predicting sustained viral response	Shaikh, S.	2012	Study design
Efficacy of prolonged tenofovir therapy on hepatitis delta in HIV-infected patients	Sierra-Enguita, R.; Vispo, E.; Barreiro, P.; De Mendoza, C.; Fernandez-Montero, J. V.; Labarga, P.; Soriano, V.	2014	Intervention
Long term follow-up of chronic hepatitis delta patients treated with pegylated interferon: HBSAG loss is associated with early virological response	Stern, C.; Castelnau, C.; Ripault, M. P.; Gault, E.; Moucari, R.; Houssel, P.; Cardoso, A. C.; Gordien, E.; Valla, D.; Marcellin, P.	2010	Study design

Quality of life in patients with various liver diseases: Patients with HCV show greater mental impairment, while patients with PBC have greater physical impairment	Tillmann, H. L.; Wiese, M.; Braun, Y.; Wiegand, J.; Tenckhoff, S.; Mössner, J.; Manns, M. P.; Weissenborn, K.	2011	Patient population not of interest
Meta-analysis: antiviral treatment for hepatitis D	Triantos, C.; Kalafateli, M.; Nikolopoulou, V.; Burroughs, A.	2012	Review
Achieving functional cure of HBV and HBV/ HDV co-infection with REP 2139: Completed follow-up in the REP 401 and REP 301-LTF studies	Vaillant, A.	2020	Comparator
HBsAg and HDV RNA reduction with REP 2139-Ca and peg-INF alpha 2a in chronic HBV/HDV infection	Vaillant, A.; Pantea, V.; Cebotarescu, V.; Cojuhari, L.; Jimbei, P.; Albrecht, J.; Schmid, P.; Krawczyk, A.; Karimzadeh, H.; Roggendorf, M.; Bazinet, M.	2016	Study design
A Phase 2 study of titrating-dose lonafarnib plus ritonavir in patients with chronic hepatitis D: Interim results from the lonafarnib with ritonavir in HDV-4 (LOWR HDV-4) Study	Wedemeyer, H.; Port, K.; Deterding, K.; Wranke, A.; Kirschner, J.; Martins, E. B.; Glenn, J.; Cornberg, M.; Manns, M. P.	2016	Study design
Lamivudine-high dose interferon combination therapy for chronic hepatitis B patients co-infected with the hepatitis D virus	Wolters, L. M.; van Nunen, A. B.; Honkoop, P.; Vossen, A. C.; Niesters, H. G.; Zondervan, P. E.; de Man, R. A.	2000	Study design
Effectiveness of different IFN-a regimens in antiviral treatment of HDV-infection	Yesmembetov, K. I.; Abdurakhmanov, D. T.; Mukhin, N. A.	2014	Study design

Polymorphisms in the IL28B gene (rs12979860, rs8099917) and the virological response to pegylated interferon therapy in hepatitis D virus patients	Yilmaz, B.; Can, G.; Ucmak, F.; Arslan, A. O.; Solmaz, I.; Unlu, O.; Düzenli, S.; Korkmaz, U.; Kurt, M.; Senates, E.	2016	Study design
Effects of polymorphisms in interferon λ 3 (interleukin 28B) on sustained virologic response to therapy in patients with chronic hepatitis D virus infection	Yilmaz, E.; Baran, B.; Soyer, O. M.; Onel, M.; Onel, D.; Ormeci, A. C.; Gokturk, S.; Evirgen, S.; Akyuz, F.; Demir, K.; Besisik, F.; Kaymakoglu, S.; Karaca, C.	2014	Study design
Hepatitis delta virus kinetics under the prenylation inhibitor lonafarnib suggest HDV-mediated suppression of HBV replication	Yurdaydin, C.; Borochov, N.; Kalkan, C.; Deb Roy, S.; Karatayli, E.; Haynes-Williams, V.; Karatayli, S. C.; Canini, L.; Uprichard, S. L.; Mihat Bozdayi, A.; Choong, I.; Cory, D.; Heller, T.; Cotler, S.; Idilman, R.; Glenn, J. S.; Dahari, H.	2016	Intervention
Optimizing the prenylation inhibitor lonafarnib using ritonavir boosting in patients with chronic delta hepatitis	Yurdaydin, C.; Idilman, R.; Choong, I.; Kalkan, C.; Keskin, O.; Karakaya, M. F.; Tuzun, A. E.; Karatayli, E.; Bozdayi, M.; Cory, D.; Glenn, J. S.	2015	Intervention
The prenylation inhibitor lonafarnib can induce post-treatment alt flares with viral clearance in patients with chronic delta hepatitis	Yurdaydin, C.; Idilman, R.; Kalkan, C.; Karakaya, F.; Kartal, A. C.; Keskin, O.; Karatayli, E.; Karatayli, S. C.; Bozdayi, A. M.; Koh, C.; Heller, T.; Glenn, J.	2016	Intervention

Exploring optimal dosing of lonafarnib with ritonavir for the treatment of chronic delta hepatitis-interim results from the lowr HDV-2 study	Yurdaydin, C.; Idilman, R.; Kalkan, C.; Karakaya, F.; Kartal, A. C.; Keskin, O.; Karatayli, E.; Karatayli, S. C.; Bozdayi, A. M.; Koh, C.; Heller, T.; Glenn, J.	2016	Intervention
The prenylation inhibitor lonafarnib can induce post-treatment viral clearance in patients with chronic delta hepatitis resulting in alt normalization and regression of fibrosis	Yurdaydin, C.; Idilman, R.; Kalkan, C.; Karakaya, M. F.; Caliskan, A.; Keskin, O.; Yurdcu, E.; Karatayli, S. C.; Bozdayi, M.; Koh, C.; et al.	2017	Intervention
A phase 2 dose optimization study of lonafarnib with ritonavir for the treatment of chronic delta hepatitis-analysis from the LOWR HDV 2 study using the robogene ® real time qPCR HDV RNA assay	Yurdaydin, C.; Idilman, R.; Keskin, O.; Kalkan, C.; Karakaya, F. M.; Caliskan, A.; Yurdcu, E.; Karatayli, S. C.; Bozdayi, M. A.; Kazempour, K.; Koh, C.; Heller, T.; Glenn, J. S.	2018	Intervention
A phase 2 dose-optimization study of lonafarnib with ritonavir for the treatment of chronic delta hepatitis-end of treatment results from the LOWR HDV-2 study	Yurdaydin, C.; Idilman, R.; Keskin, O.; Kalkan, C.; Karakaya, M. F.; Caliskan, A.; Yurdcu, E.; Karatayli, S. C.; Bozdayi, M.; Koh, C.; Heller, T.; Glenn, J.	2017	Intervention
Subanalysis of the LOWR HDV-2 study reveals high response rates to Lonafarnib in patients with low viral loads	Yurdaydin, C.; Kalkan, C.; Karakaya, F.; Caliskan, A.; Karatayli, S.; Keskin, O.; Idilman, R.; Bozdayi, M.; Koh, C.; Heller, T.; Glenn, J.	2018	Intervention
Hepatitis delta in patients hospitalized in Spain (1997-2018)	Ramos-Rincon J.-M., Pinargote H., Ramos-Belinchón C., de Mendoza C., Aguilera A., Soriano V.	2021	Study design

Poor clinical and virological outcome of nucleos(t)ide analogue monotherapy in HBV/HDV co-infected patients	Scheller L., Hilgard G., Anastasiou O., Dittmer U., Kahraman A., Wedemeyer H., Deterding K.	2021	Study design
Early virological response in six patients with hepatitis D virus infection and compensated cirrhosis treated with Bulevirtide in real-life	Asselah T., Loureiro D., Le Gal F., Narguet S., Brichler S., Bouton V., Abazid M., Boyer N., Giuly N., Gerber A., Tout I., Maylin S., Bed C.M., Marcellin P., Castelnau C., Gordien E., Mansouri A.	2021	Study design
Chronic hepatitis D associated with worse patient-reported outcomes than chronic hepatitis B	Buti M., Stepanova M., Palom A., Riveiro-Barciela M., Nader F., Roade L., Esteban R., Younossi Z.	2021	Copy duplicate from original SLR
Residual low HDV viraemia is associated HDV RNA relapse after PEG-IFNa-based antiviral treatment of hepatitis delta: Results from the HIDIT-II study	Bremer B., Anastasiou O.E., Hardtke S., Caruntu F.A., Curescu M.G., Yalcin K., Akarca U.S., Gürel S., Zeuzem S., Erhardt A., Lüth S., Papatheodoridis G.V., Radu M., Idilman R., Manns M.P., Cornberg M., Yurdaydin C., Wedemeyer H.	2021	Copy duplicate from original SLR
A transient early HBV-DNA increase during PEG-IFNα therapy of hepatitis D indicates loss of infected cells and is associated with HDV-RNA and HBsAg reduction	Anastasiou O.E., Yurdaydin C., Maasoumy B., Hardtke S., Caruntu F.A., Curescu M.G., Yalcin K., Akarca U.S., Gürel S., Zeuzem S., Erhardt A., Lüth S., Papatheodoridis G.V., Radu M., Liebig S., Bantel H., Bremer B., Manns M.P., Cornberg M., Wedemeyer H.	2021	Copy duplicate from original SLR

Ten-year follow-up of a randomized controlled clinical trial in chronic hepatitis delta	Wranke A., Hardtke S., Heidrich B., Dalekos G., Yalçin K., Tabak F., Gürel S., Çakaloğlu Y., Akarca U.S., Lammert F., Häussinger D., Müller T., Wöbse M., Manns M.P., Idilman R., Cornberg M., Wedemeyer H., Yurdaydin C.	2020	Copy duplicate from original SLR
Long-term clinical outcomes in patients with chronic hepatitis delta: the role of persistent viraemia	Palom A., Rodríguez-Tajes S., Navascués C.A., García-Samaniego J., Riveiro-Barciela M., Lens S., Rodríguez M., Esteban R., Buti M.	2020	Study design
Efficacy and safety of bulevirtide in the treatment of chronic hepatitis d: Results of randomized controlled trials	Bogomolov P.O., Ivashkin V.T., Bueverov A.O., Syutkin V.E., Sagalova O.I., Sleptsova S.S., Yushuk N.D., Gusev D.A., Zhdanov K.V., Chulanov V.P.	2020	Language
Prevalence of hepatitis D among patients with hepatitis B viral infection attending a tertiary care centre of Nepal	Regmi K., Shrestha J.K., Sudhamshu K.C., Jaishi B., Karki N., Khadka D., Khadka S.	2017	Study design
Treatment of chronic hepatitis delta virus with peg-interferon and factors that predict sustained viral response	Samiullah S., Bikharam D., Nasreen	2012	Study design
Peginterferon plus adefovir versus either drug alone for hepatitis delta	Wedemeyer H., Yurdaydìn C., Dalekos G.N., Erhardt A., Çakaloğlu Y., Değertekin H., Gürel S., Zeuzem S., Zachou K., Bozkaya H., Koch A., Bock T., Dienes H.P., Manns M.P.	2011	Copy duplicate from original SLR

Safety and efficacy of 2mg bulevirtide in patients with chronic hbv/hdv co-infection. first real-world results (french early access program).	De Ledinghen V., Guyader D., Metivier S., Hilleret M.-N., Fontaine H., Roche B., Carrie N.G., Alteroche L.D., Ratti V.L., Gervais A., Stern C., Alric L., Hubert I.F., Asselah T., Lacombe K., Zoulim F., Dumortier J., Franza A.M., Lascoux-Combe C., Muti L., Hourmand I.O., Larrey D., Leroy V., Rosa I., Chas J., Heluwaert F., Borentain P., Mabile I.A., Prouvost-Keller B., Ahmed S.N.S., Roulot-Marullo D.	2021	Study design
Hepatitis d-associated hospitalizations in the united states: 2010-2018	Wasuwanich P., Striley C.W., Kamili S., Teshale E.H., Seaberg E.C., Karnsakul W.	2021	Study design
Rare cases of non-response in bulevirtide (blv) treated patients from the myr-204/301 studies are not associated with the development of blv resistance.	Hollnberger J., Schlund F., Schöneweis K., Zehnder B., Urban S.	2021	Study design
Treatment with bulevirtide improves patient reported outcomes in patients with chronic hepatitis delta (chd): An interim exploratory analysis at week 24	Wedemeyer H., Aleman S., Chulanov V., Hilgard G., Antonova J., Kaushik A.M., Lloyd A., Manuilov D., Suri V., Tran T.T., Osinusi A.O., Lampertico P., Morozov V., Sagalova O., Stepanova T., Buti M.	2021	Study design
Efficacy of pegylated interferon-alpha-2a in chronic hepatitis D-infected patients. Experience from the tertiary care hospital in Karachi	Nazish B., Hussain R., Lajpat R., Hanisha K.	2021	Study design

48 weeks of high dose (10 mg) bulevirtide as monotherapy or with peginterferon alfa-2a in patients with chronic HBV/HDV co-infection	Wedemeyer H., Schöneweis K., Bogomolov P.O., Chulanov V., Stepanova T., Viacheslav M., Allweiss L., Dandri M., Ciesek S., Dittmer U., Haefeli W.-E., Alexandrov A., Urban S.	2020	Copy duplicate from original SLR
Residual low HDV viremia is associated with HDV RNA relapse after PEG-IFNa-based antiviral treatment of hepatitis D (delta): results from the HIDIT-II study	Bremer B., Anastasiou O., Hardtke S., Caruntu F.A., Curescu M.G., Yalcin K., Akarca U.S., Gurel S., Idilman R., Zeuzem S., Erhardt A., Lüth S., Papatheodoridis G., Radu M., Manns M.P., Cornberg M., Yurdaydin C., Wedemeyer H.	2020	Copy duplicate from original SLR
Poor clinical and virological outcome of nucleos(t)ide therapy in HBV/HDV co-infected patients	Scheller L., Hilgard G., Anastasiou O.A., Dittmer U., Kahraman A., Wedemeyer H., Deterding K.	2020	Study design
A phase 2 dose-finding study of lonafarnib and ritonavir with or without interferon alpha for chronic delta hepatitis	Yurdaydin C, Keskin O, Yurdcu E, Çalişkan A, Önem S, Karakaya F, Kalkan Ç, Karatayli E, Karatayli S, Choong I, Apelian D, Koh C, Heller T, Idilman R, Bozdayi AM, Glenn JS.	2021	Study design

Abbreviations: SLR = systematic literature review

H.1.5 Quality assessment

The study's strengths include the systematic and transparent approach to study identification and selection and the use of two independent data extractors to ensure the accuracy of recorded data. Furthermore, the SLR methods were designed to adhere to internationally recognised guidance documents, including PRISMA, the Cochrane review handbook, and the NICE requirements. Further, the SLR was conducted from a global perspective and can be easily adapted for submission to any market.

The limitations of the SLR lie primarily in the design differences of the included randomised controlled trials (RCTs): internal and external validity of each trial, as well as the heterogeneity of trial and subject characteristics across trials. The actual impact of differences in design and characteristics between bulevirtide and interferon studies will be analysed during the feasibility step before direct or network meta-analysis is performed if deemed feasible.

H.1.6 Unpublished data

Not applicable.

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

I.1 Health-related quality-of-life search

The HRQoL used in the application was based on the clinical trial and a published meta-analysis of utilities. This section is therefore not relevant and has been left blank.

Table 102 Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	Embase.com		dd.mm.yyyy
Medline	Ovid		dd.mm.yyyy
Specific health economics databases[1]			dd.mm.yyyy

Abbreviations:

Table 103 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
e.g. NICE	www.nice.org.uk		dd.mm.yyyy
CEA Registry	Tufts CEA - Tufts CEA		dd.mm.yyyy

Table 104 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
Conference name	e.g. conference website	Electronic search	List individual terms used to search in the congress material:	dd.mm.yyyy

[1] Papaioannou D, Brazier J, Paisley S. Systematic searching and selection of health state utility values from the literature. Value Health. 2013;16(4):686-95.

	Journal supplement [insert reference]	Skimming through abstract collection	dd.mm.yyyy

I.1.1 Search strategies

Table 105 Search strategy for [name of database]

No.	Query	Results
#1		88244
#2		85778
#3		115048
#4		7011
#5		10053
#6		12332
#7		206348
#8		211070
#9	#7 OR #8	272517
#10	#3 AND #6 AND #9	37

I.1.2 Quality assessment and generalizability of estimates

I.1.3 Unpublished data

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

J.1 External literature for input to the health economic model

This SLR aimed to compile evidence on economic evaluations and costs and resource use of pharmacological treatments for adults with CHD in support of the development of local reimbursement submissions for bulevirtide.

Detailed information regarding how the literature for the model was identified is provided in Appendix I.1 and Appendix I.1.1.

Table 106 Sources included in the economic search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	Embase.com	1974 to July 2024	08.07.2024
Medline	pubmed.ncbi.nlm.nih.gov	1946 to July 2024	08.07.2024
CENTRAL	Wiley platform	Inception to July 2024	08.07.2024
CDSR	Wiley platform	2020 to March 2021	30.03.2021
NHS EED	CRD interface	2021 to July 2024	08.07.2024

Abbreviations: Abbreviations: CDSR = Cochrane Database of Systematic Reviews; EED = Economic Evaluation Database

J.1.1 Results

The inclusion and exclusion criteria used to assess the relevance of titles, abstracts and full-texts for the economic and resource use SLR is presented in Table 89. Eligibility for inclusion was defined using the PICOS (Population, Intervention, Comparators, Outcome, Study design) approach and publications reviewed using eligibility flowcharts. Studies were selected as followed:

- Each title and abstract was reviewed against the eligibility criteria by two independent reviewers. Where the applicability of the inclusion criteria was unclear, the article was included at this stage to ensure that all potentially relevant studies were captured. The results of the two reviewers were compared and any disagreements resolved by discussion until a consensus was met. If necessary, a third independent reviewer arbitrated the final decision.
- Full text publications of records included at abstract stage were then reviewed against the eligibility criteria by two independent reviewers. In cases where the publication did not give enough information to be sure it met the eligibility criteria, the publication was excluded at this stage to ensure that only relevant publications

were ultimately included in the SLR. The results of the two reviewers were compared and any disagreements resolved by discussion until a consensus was met. If necessary, a third independent reviewer arbitrated the final decision.

Table 107 Inclusion and exclusion criteria used for assessment of studies

	Inclusion criteria	Exclusion criteria
Population	Patients ≥18 years old with chronic HDV who have compensated liver disease	• Patients without chronic hepatitis delta • Patients with chronic hepatitis delta who have decompensated liver disease • Patients <18 years old Mixed populations for which outcomes for adults with HDV are not presented separately
Intervention	Any intervention or combination of interventions given for the treatment of chronic hepatitis delta infection (including but not limited to bulevirtide, PEG-IFNα, IFNα)	Studies that do not investigate one of the interventions of interest in at least one of the arms.
Comparators	No restrictions	N/A
Outcomes	Measures of costs and resource use: • Direct costs e.g. hospitalisation costs, treatment costs, non-hospital care costs, administration costs • Indirect costs e.g. productivity loss • Resource use e.g. drug use Cost-effectiveness outcomes, including but not limited to: • Incremental cost-effectiveness ratios • Cost per outcome • Quality adjusted life years • Disability-adjusted life year • Life-years gained • Total costs	Studies not presenting relevant outcomes for the population of interest

Study design/publication type	• Cost-effectiveness analysis • Cost-utility analysis • Cost-minimisation analysis [Cost-comparison analysis] • Cost-consequence analysis • Cost-benefit analysis • Cost-offset analysis • Budget impact analysis • Any studies reporting original cost and/or resource use data	• Reviews/editorials/commentaries/letters • Case reports • Pharmacodynamic/pharmacokinetic studies
Language restrictions	English language studies[a]	Non-English title and abstract or non-English publications where relevant results are not presented in the abstract

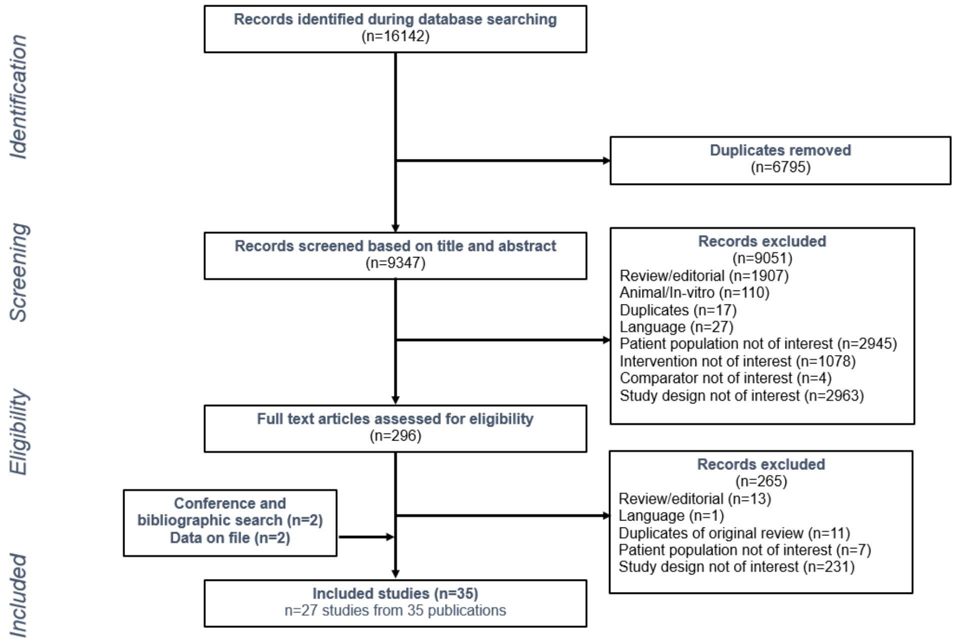
[a]English abstracts of non-English language studies were considered for inclusion.

Abbreviations: HDV = Hepatitis D virus; N/A = not applicable; PEG-IFNα = Pegylated Interferon alpha

A total of 16142 records were retrieved by the electronic database searches from inception of the databases. After deduplication of results, 9347 unique records were suitable for review. Following title and abstract review, 296 records were selected for full text review. Of these, 31 were found to fulfil the eligibility criteria for inclusion in the review. Two records were identified from the supplementary searches of congresses, HTA body and economic websites and SLR bibliographies and two studies were available as data on file.

In total, 35 publications reporting on 27 unique studies were included in this review. A PRISMA diagram showing the flow of records through each stage of the review process is presented in Figure 25.

Figure 33 PRISMA flow for the economic SLR from inception to 8th July 2024



Abbreviations: SLR = systematic literature review

A complete list of all included studies is provided in Table 90.

Table 108 Complete list of included studies in the economic SLR

Title	Author	Year
HBV-infections in Germany – health care costs in a real-lifesetting	Stahmeyer, J. T.; Becker, H.; Orlemann, A. L.; Krauth, C.; Manns, M.; Wedemeyer, H.	2017
HBV-infection in Germany-costs in a real-life setting	Becker, H.; Stahmeyer, J. T.; Orlemann, A. L.; Krauth, C.; Manns, M.; Wedemeyer, H.	2016
Role of lamivudine in the posttransplant prophylaxis of chronic hepatitis B virus and hepatitis delta virus coinfection	Caccamo, L.; Agnelli, F.; Reggiani, P.; Maggi, U.; Donato, M. F.; Gatti, S.; Paone, G.; Melada, E.; Rossi, G.	2007
Disease and economic burdens of hepatitis delta in The United States	Elsaid, M.; Narayanan, N.; Li, Y.; Rustgi, V. K.	2018
Economic and Health Care Burdens of Hepatitis Delta: A Study of Commercially Insured Adults in the United States	Elsaid, M. I.; Li, Y.; John, T.; Narayanan, N.; Catalano, C.; Rustgi, V. K.	2020
Healthcare cost and utilization in hepatitis delta: Analysis of privately insured patients in The United States	Elsaid, M. I.; Li, Y.; Ram Pentakota, S.; John, T.; Catalano, C.; Rustgi, V. K.	2019
Recognizing the impact of endemic hepatitis D virus on hepatitis B virus eradication	Goyal, A.; Murray, J. M.	2016

Cost-Effectiveness of Peg-Interferon, Interferon and Oral Nucleoside Analogues in the Treatment of Chronic Hepatitis B and D Infections in China	Goyal, A.; Murray, J. M.	2016
Screening for hepatitis D and PEG-Interferon over Tenofovir enhance general hepatitis control efforts in Brazil	Goyal, A.; Romero-Severson, E. O.	2018
Adaptation and Calibration of a Markov MODEL Framework in Hepatitis D	Ouared, C; Massetti, M; Brandt, A S; Kozaris, T; Leleu, H.	2020
Clinical and economic aspects of bulevirtide use in patients with chronic hepatitis d	Frolov M.Y., Rogov V.A., Salasyuk A.S., Chulanov V.P., Bogomolov P.O.	2020
Characteristics, healthcare resource utilization, and costs among Medicaidinsured adults with hepatitis delta virus: An analysis of US all-payer medical and pharmacy claims data	Maughn K., Achter E., Liu Y.	2022
CO150 Characteristics, Healthcare Resource Utilization and Costs Among Medicaid-Insured Adults With Hepatitis Delta Virus: An Analysis of US All-Payer Medical and Pharmacy Claims Data	Maughn K., Achter E., Liu Y.	2022
Healthcare resource utilization and costs of hepatitis delta in the United States: an analysis of all-payer claims database	Lim J., Rustgi V., Gish R.G., Jacobson I.M., Kaushik A., Liu Y., Acter E., Wong R.	2022
Evaluating Hepatitis Delta Virus Disease Prevalence and Patient Characteristics Among Hospitalized Adults in Italy	Lampertico P., Perrone V., Sangiorgi D., Giacomini E., Degli Esposti L., Kim C.H., Kaushik A.M.	2022
Healthcare resource utilization and costs among hospitalized hepatitis delta patients in Italy: An analysis of Italian administrative databases	Lampertico P., Perrone V., Sangiorgi D., Giacomini E., Esposti L.D., Kim C.H., Kaushik A.M.	2022

Understanding the Natural History of Chronic Hepatitis D: Proposal of a Model for Cost-Effectiveness Studies	Kaushik A., Dusheiko G., Kim C., Smith N.J., Kinyik-Merena C., Di Tanna G.L., Wong R.J.	2024
Real-world analysis of healthcare resource utilization and costs among diagnosed hepatitis D patients within the outpatient setting in Italy	Kaushik A., Lampertico P., Perrone V., Sangiorgi D., Dovizio M., Degli Esposti L., Kim C.	2023
Patients with CHD coinfection have greater comorbidities, higher healthcare resource use and costs than CHB monoinfection-results from a Spanish national hospital database	Buti M., Kaushik A., Ascanio M., Darba J., Kachru N.	2022
Rising clinical and economic burden among hepatitis D patients who attended Spanish hospitals	Buti M., Kaushik A., Ascanio M., Darba J., Kachru N.	2022
Health Care Resource Utilization and Costs of HDV Infection vs HBV Monoinfection Across Disease States in a Hospital Records Database From Spain	Buti M., Rock M., Ascanio M., Darba J., Kim C.H.	2023
Impact of hepatitis D reflex testing on the future disease burden: A modelling analysis	Buti M., Domínguez-Hernández R., Palom A., Esteban R., Casado M.Á.	2023
Impact of the anti-HDV reflex testing on the reduction of hepatitis D burden in Spain	Buti M., Domínguez-Hernández R., Palom A., Rando-Segura A., Barciela M.R., Esteban R., Rodríguez-Frías F., Casado M.Á.	2023
Bulevirtide avoids future clinical events and related costs compared to pegylated-interferon alpha in chronic hepatitis D in Spain	Buti M., Calleja Panero J.L., Rodríguez Sagrado M.Á., Cantero H., de las Heras A., Domínguez-Hernández R., Casado M.Á.	2022
Real-World Epidemiology, Treatment Patterns, and Disease Burden of Chronic Hepatitis B and HDV Co-Infection in South Korea	Cho Y., Park S.B., Park S.Y., Choi W.J., Kim B., Han H.	2023

Hepatitis D-associated hospitalizations in the United States: 2010–2018	Wasuwanich P., Striley C.W., Kamili S., Teshale E.H., Seaberg E.C., Karnsakul W.	2022
Hepatitis delta in patients hospitalized in Spain (1997-2018)	Ramos-Rincon J.-M., Pinargote H., Ramos-Belinchón C., De Mendoza C., Aguilera A., Soriano V.	2021
Healthcare resource use and costs associated with hepatitis delta virus infection compared to hepatitis B virus monoinfection among commercially insured patients in the US	Wong R., Gish R.G., Kim C., Leung G., Jacobson I.M., Lim J., Kaushik A.	2023
Significantly higher clinical and economic burden following diagnosis of hepatitis delta virus infection among commercially insured adults with chronic hepatitis B in the United States	Wong R., Gish R.G., Kim C., Leung G., Jacobson I.M., Lim J., Kaushik A.	2023
What is the additional cost of each anti HDV positive case detected through reflex testing	Domínguez-Hernández R., Palom A., Rando-Segura A., Rodriguez-Frías F., Barciela M.R., Casado M.Á., Esteban-Mur R., Buti M.	2022
Qualitative analysis of the patient journey: HDV management in rural and urban settings of Mongolia	Nandintsetseg T., Bat-Osor U.	2022
HEPCLUDEX (bulévirtide)	-	2020
Benefit assessment of the active ingredient "Bulevirtide"	-	2020
Hepatitis d-associated hospitalizations in the united states: 2010-2018	Wasuwanich P., Striley C.W., Kamili S., Teshale E.H., Seaberg E.C., Karnsakul W.	2021

Hepatitis delta in patients hospitalized in Spain (1997-2018)	Ramos-Rincon J.-M., Pinargote H., Ramos-Belinchón C., de Mendoza C., Aguilera A., Soriano V.	2021

Abbreviations: SLR = systematic literature review

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