NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Bulevirtide for treating chronic hepatitis D [ID3732]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL (STA)

Bulevirtide for treating chronic hepatitis D [ID3732]

Contents:

The following documents are made available to consultees and commentators. The **final scope** and **final stakeholder list** are available on the NICE website.

Pre-technical engagement documents

1. **Company submission from Gilead Sciences**

2. **Clarification questions and company responses**
   a. Clarification question response
   b. Clarification question response appendix

3. **Patient group, professional group and NHS organisation submissions from:**
   a. British Association for Sexual Health and HIV
   b. Royal College of Pathologists
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4. **External Assessment Group report** prepared by BMJ Group

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Post-technical engagement documents

6. **Technical engagement response from company**
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8. **External Assessment Group critique of company response to technical engagement** prepared by BMJ Group
   a. EAG technical engagement response form
   b. EAG technical engagement response report
   c. EAG technical engagement response report addendum

9. **Data on the epidemiology of HDV infection in the UK** prepared by UKHSA

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Bulevirtide for treating chronic hepatitis D [ID3732]

Document B

Company evidence submission

April 2022

File name	Version	Contains confidential information	Date
ID3732_Bulevirtide_CHD_Document B_FINAL 25.04.22 [ACIC]	**1.0**	**Yes**	**25/04/22**

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Tables and figures

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Abbreviations

µg	Microgram
AASLD	American Association for the Study of Liver Diseases
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BLV	Bulevirtide
BMI	Body mass index
BSC	Best supportive care
CC	Compensated cirrhosis
CEAC	Cost-effectiveness acceptability curve
CfB	Change from baseline
CHB	Chronic hepatitis B
CHD	Chronic hepatitis delta
CG	Clinical guidelines
CI	Confidence interval
CRD	Centre for Reviews and Dissemination
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events
d	Day
DCC	Decompensated cirrhosis
DMA	Direct meta-analysis
DT	Delayed treatment
EASL	European Association for the Study of the Liver
EC	European Commission
ECG	Electrocardiogram
EMA	European Medicines Agency
EOS	End of study
EPAR	European public assessment report
EQ-5D	EuroQoL-5 Dimension
EQ-5D-3L	EuroQoL-5 Dimension 3 Levels
FACIT-F	Functional assessment of chronic illness therapy-fatigue
FAS	Full analysis set
FDA	Food and Drug Administration
GGT	Gamma-glutamyl transferase
GSI	Gilead Sciences, Inc.
HBeAg	Hepatitis B e-antigen
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCRU	Healthcare resource utilisation
HCV	Hepatitis C virus

HDAg	Hepatitis delta antigen
HDV	Hepatitis delta virus
HIV	Human immunodeficiency virus
HQLQ	Hepatitis Quality of Life Questionnaire™
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
ICF	Informed consent form
IFN	Interferon
IPD	Individual patient data
IQR	Interquartile range
kPa	Kilopascal
LOCF	Last observation carried forward
LOD	Limit of detection
LT	Liver transplantation
LYG	Life years gained
MedDRA	Medical Dictionary for Regulatory Activities
MEF	Missing equals failure
mg	Milligram
MHRA	Medicines and Healthcare products Regulatory Agency
mITT	Modified intention-to-treat
n/miss	Number of patients with evaluable/missing data
NA	Nucelos(t)ide analogue
NC	Non-cirrhotic
NHB	Net health benefit
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NTCP	Sodium taurocholate co-transporting polypeptide
OLS	Ordinary least squares
ONS	Office for National Statistics
OR	Odds ratio
OWSA	One-way deterministic sensitivity analysis
PAS	Patient access scheme
PCR	Polymerase chain reaction
PEG-IFN	Peginterferon alfa-2a
PIM	Promising innovative medicine
PLT	Post-liver transplant
PO	Per oral
PP	Per protocol
PPAS	Per protocol analysis set
PRO	Patient reported outcome
PSA	Probabilistic sensitivity analysis
Q1	First quartile
Q3	Third quartile

QALY	Quality-adjusted life year
QoL	Quality of life
RNA	Ribonucleic acid
SAE	Serious adverse event
SAS	Safety analysis set
SC	Subcutaneous
SD	Standard deviation
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
TDF	Tenofovir
TEAE	Treatment-emergent adverse event
UK	United Kingdom
ULN	Upper limit of normal
VAS	Visual Analogue Scale
VR	Virologic resistance
WK	Weekly
WPAI	Work productivity and activity impairment
WTP	Willingness-to-pay

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The submission focuses on part of the technology's marketing authorisation, specifically adults with chronic hepatitis delta (CHD) who have compensated liver disease, and evidence of significant fibrosis (METAVIR stage greater than or equal to F2), whose disease has responded inadequately to interferon-based therapy (hereafter referred to as IFN-based therapy), or who are ineligible to receive IFN-based therapy due to intolerance or contraindication. Bulevirtide has received conditional marketing authorisation from the Medicines and Healthcare products Regulatory Agency (MHRA) for the treatment of chronic hepatitis delta virus (HDV) infection in plasma (or serum) HDV-RNA positive adults with compensated liver disease. It should be noted that based on the anticipated positioning of bulevirtide within the UK treatment pathway, this submission appraises the clinical and cost-effectiveness of bulevirtide in a narrower population than that defined in the final scope issued by NICE.

The proposed position in the treatment pathway is narrower than the marketing authorisation because:

- This is relevant to NHS clinical practice and the anticipated positioning of bulevirtide within the UK treatment pathway.
- This position reflects where bulevirtide treats the population with the highest unmet need i.e., where IFN-based therapy is not a treatment option.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with CHD who have compensated liver disease.	Adults with CHD who have compensated liver disease, and evidence of significant fibrosis (METAVIR stage greater than or equal to F2), whose disease has responded inadequately to IFN-based therapy, or who are ineligible to receive IFN-based therapy due to intolerance or contraindication.	This positioning addresses the area of highest unmet need in the treatment of hepatitis delta. Where IFN-based therapy e.g., PEG-IFN, is recommended by NICE clinical guideline CG165 but is not an option, either due to failure to respond, contraindication, or intolerance, no alternative treatment options exist.
Intervention	Bulevirtide.	Bulevirtide.	Not applicable.
Comparator(s)	• Best supportive care (BSC). • Peginterferon alfa-2a.	• Best supportive care.	Bulevirtide is the first and only approved treatment for CHD. Whilst it is acknowledged that IFN-based therapy is used off-label for some patients, in the absence of IFN-based the only treatment option is BSC, generally defined as symptomatic treatment, alongside treatment for the underlying hepatitis B. In the population proposed, BSC is the appropriate comparator.
Outcomes	The outcome measures to be considered include: • Virological response.	The outcome measures to be considered include: • Virological response.	The outcome 'development of resistance to treatment' will not be presented in the company submission.

	• Biochemical response. • Sustained response. • Development of resistance to treatment. • Mortality. • Adverse effects of treatment. • Health-related quality of life.	• Biochemical response. • Mortality. • Adverse effects of treatment. • Health-related quality of life.	This was not an endpoint in the pivotal MYR 301 trial, and as such limited evidence exists to support this endpoint. The outcome 'sustained response' will not be presented in the company submission. It relates to continued virologic response post treatment completion. As bulevirtide is a chronic therapy with no licensed stopping rules (beyond futility) there is no possibility of 'sustained response'.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes	Not applicable.

	between the technologies being compared. Costs will be considered from NHS and Personal Social Services Perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The use of bulevirtide is conditional on the presence of HDV. The economic modelling should include costs associated with diagnostic testing for HDV in people with hepatitis B who would not otherwise have been tested. A sensitivity analysis should be provided without the costs of the diagnostic test.	between the technologies being compared. Costs will be considered from NHS and Personal Social Services Perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The use of bulevirtide is conditional on the presence of HDV. NICE clinical guideline CG165 states that all adults who are HBsAg positive (i.e., hepatitis B virus (HBV) infected) should be tested for hepatitis delta virus antibody (anti-HDV). A positive anti-HDV result must then be followed by a HDV ribonucleic acid (RNA) test, alongside liver fibrosis staging, in order to determine those patients currently infected with HDV who should be offered the 48-week course of PEG-IFN	

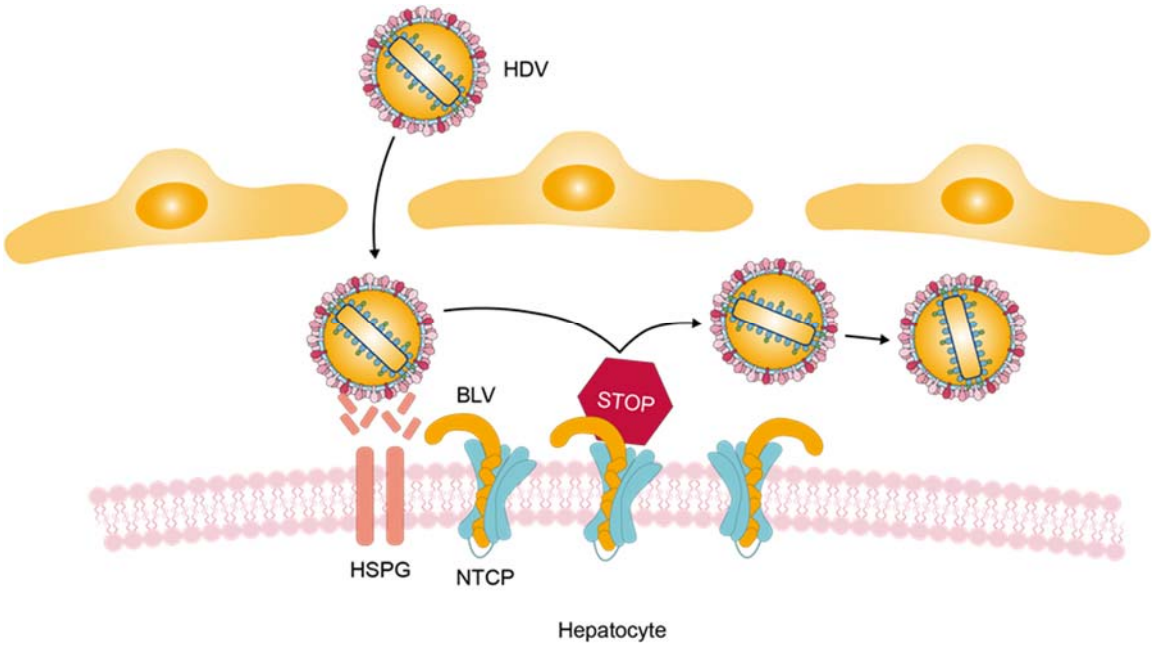
		recommended in NICE clinical guideline CG165. As such, there are no additional diagnostic tests required for the population who are within the economic modelling presented herein.	
Subgroups to be considered	Not applicable.	• People with cirrhosis (METAVIR fibrosis stage F4). • People without cirrhosis (METAVIR fibrosis stage F0-F3).	We propose analysing outcomes in patients with and without cirrhosis. The development of cirrhosis is associated with a substantial clinical burden, with people with cirrhosis having a higher probability of developing severe liver complications and lower overall survival compared to those without cirrhosis.
Special considerations including issues related to equity or equality	If the evidence allows the following subgroups should be considered: • Severity of disease.	If the evidence allows the following subgroups should be considered: • Severity of disease, as defined by the METAVIR fibrosis stage.	Not applicable.

Key: BSC: best supportive care; CG: clinical guidelines; CHD: chronic hepatitis delta; HBsAg; hepatitis b surface antigen; HDV: hepatitis delta virus; IFN: interferon; PEG-IFN: peginterferon alfa-2a; RNA: ribonucleic acid.

B.1.2 Description of the technology being evaluated

Bulevirtide, formerly known as Myrcludex B, is a novel, first-in-disease and first-in-class entry inhibitor that binds specifically to the sodium taurocholate co-transporting peptide (NTCP) and acts as a potent, highly selective entry inhibitor of HDV into hepatocytes (1,2). Bulevirtide does not directly interfere with viral production or elimination of the virus, and instead acts as a post-attachment step, likely misdirecting the entry route of HDV to an unproductive cellular pathway (Figure 1). By blocking the essential entry receptor, the de novo infection of hepatocytes 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 (3–5).

Figure 1: Bulevirtide mechanism of action



Key: BLV: bulevirtide; HDV: hepatitis delta virus; HSPG: heparan sulphate proteoglycan; NTCP: sodium taurocholate co-transporting polypeptide.
Source: MYR Pharmaceuticals. Mechanism of Action (6)

In June 2015, bulevirtide was granted orphan designation (EU/3/15/1500) by the European Commission (EC) because of the seriousness of HDV infection, the lack of licensed treatment options, and the rarity of HDV infection (7). Bulevirtide (2 mg given subcutaneously [SC] once daily) was subsequently granted conditional marketing authorization for the treatment of CHD in adults with compensated liver

disease under the brand name HEPCLUDEX® in Europe (7), representing an important step towards addressing the current unmet needs in CHD as the first approved treatment for this indication.

Table 2 provides an overview of the technology being evaluated. The Summary of Product Characteristics (SmPC) is included in Appendix C1.1 SmPC (8).

Table 2: Technology being evaluated

UK approved name and brand name	Bulevirtide (HEPCLUDEX®)
Mechanism of action	Bulevirtide blocks the entry of HDV into hepatocytes by binding to and inactivating an essential HDV entry receptor described as an NTCP receptor. Given this mechanism of action, bulevirtide does not prevent continued HDV replication within previously infected cells, or the release of HDV virus into the blood stream. Rather, it prevents infection of new hepatocytes. As a result, reduction in HDV RNA in the blood is a slower process than observed with treatments for hepatitis C virus (HCV), as it relies on the immune system killing cells already infected whilst bulevirtide prevents new cells being infected. As the number of infected cells in the liver declines over time, the HDV viral load in the blood also declines.
Marketing authorisation/CE mark status	Bulevirtide received conditional marketing authorisation (reliance model) from the MHRA on November 16th, 2021 (8). Bulevirtide was awarded Promising Innovative Medicine (PIM) designation by the MHRA in March 2019.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Bulevirtide is indicated for CHD infection in plasma (or serum) HDV RNA-positive adult patients with compensated liver disease.

Method of administration and dosage	Bulevirtide is presented as a lyophilized powder in sterile vials with a nominal content of 2 mg and is intended for SC injection. The vial content must be reconstituted using 1.0 ml of sterile water-for-injection, as a single dose prior to administration and administered into the upper thigh or abdomen. The recommended dose and treatment duration of bulevirtide is 2 mg once daily (every 24 hours ± 4 hours) by SC injection as monotherapy or in co-administration with a nucleos(t)ide analogue (NA) for treatment of underlying HBV infection.
Additional tests or investigations	Not applicable.
List price and average cost of a course of treatment	List price: [redacted] per pack of 30 vials of 2 mg powder for solution for injection. The optimal treatment duration is unknown. Treatment should be continued as long as associated with clinical benefit (see SmPC for further details).
Patient access scheme (if applicable)	A patient access scheme (PAS) has been approved by PASLU for NHSE&I. This PAS involved a simple [redacted] discount from list price. The confidential net price is [redacted] per pack.

Key: CHD: chronic hepatitis delta; EMA: European Medicines Agency; HBV: hepatitis B virus; HDV: hepatitis delta virus; MHRA: Medicines and Healthcare products Regulatory Agency; NTCP: sodium-taurocholate co-transporting polypeptide; PAS: patient access scheme; RNA: ribonucleic acid; NA: nucleos(t)ide analogue; SC: subcutaneous.

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Disease overview

Hepatitis delta represents the most severe form of viral hepatitis (4,9). Hepatitis delta is caused by HDV, a defective RNA virus that requires the presence of the hepatitis B surface antigen (HBsAg) for its complete replication and transmission. As such, this form of hepatitis only occurs in individuals who are also infected with the hepatitis B virus (HBV) (10).

Hepatitis delta can cause acute or fulminant hepatitis (11), and occurs either as a coinfection with HBV, which can be self-limiting, or as a superinfection in a patient with chronic hepatitis B (CHB) infection (12). The majority (52.0%) of people suffering from acute hepatitis delta will develop CHD, of which 76% will develop chronic hepatitis. In some people with hepatitis delta, the progression to chronic hepatitis occurs quickly, with 39.2% of people with acute infection developing chronic hepatitis within 1.5 years on average (10). People with chronic hepatitis display an array of clinical manifestations, ranging from non-specific symptoms to rapidly progressing hepatitis. People with hepatitis delta may not display any obvious symptoms until liver function is compromised, and this can mean that diagnosis is often fortuitous or may follow the appearance of late complications (13), especially if the NICE hepatitis B (chronic) clinical guideline CG165, which stipulates that adults who are HBsAg positive should be tested for anti-HDV.

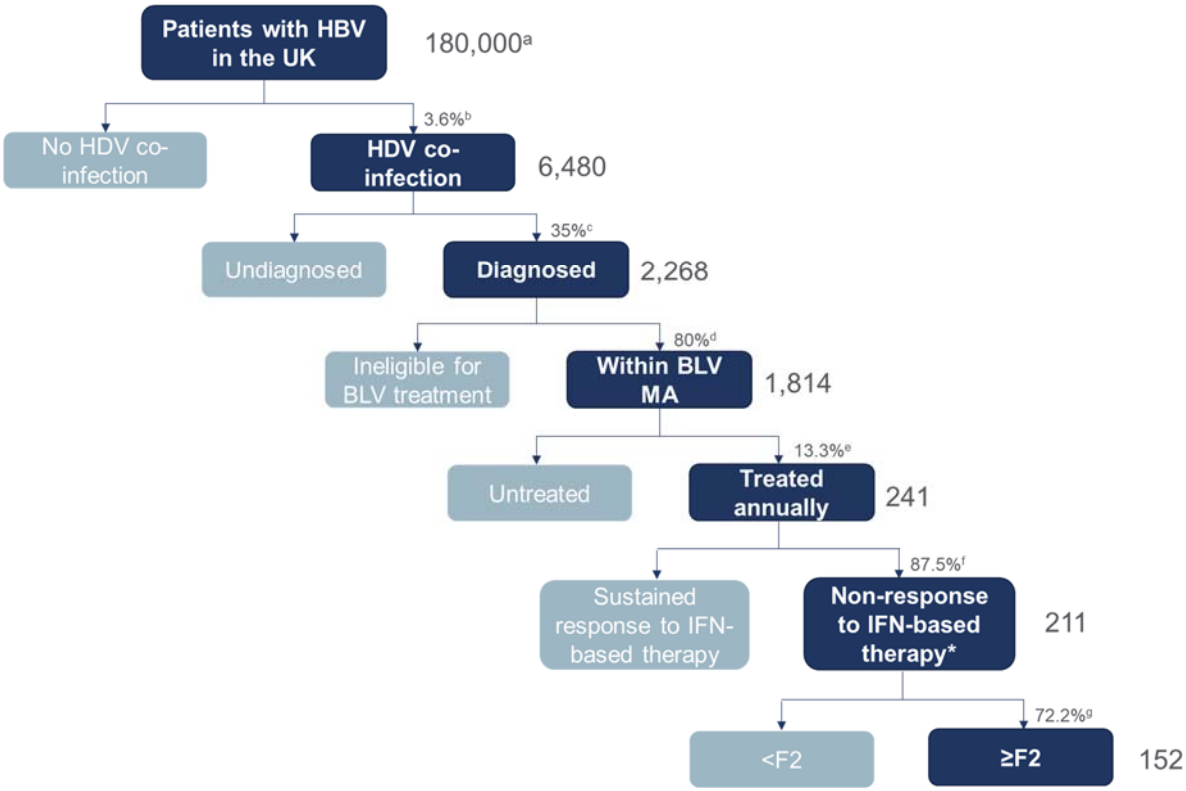
CHD is defined as an infection lasting ≥6 months (14,15). Rates of disease progression, including liver-related events, cirrhosis, hepatocellular carcinoma (HCC) and death, are greater with CHD than for patients with CHB monoinfection (16). Several cohort studies have found that this risk may be as much as nine times higher than in CHB monoinfected patients (17). Approximately 70% of patients with CHD develop cirrhosis within 5-10 years (18), with cirrhotic patients at a three-fold greater risk of developing HCC, and a two-fold greater risk of mortality, than HDV-negative cirrhotic patients (19). Overall mortality rates as a result of CHD have been observed at 11% within the first six months of the disease (10), and as high as 50% within five

years for cirrhotic patients (10,20). Therefore, development of cirrhosis and HCC is linked to increased morbidity and mortality, and early treatment of CHD is advantageous, as it could slow disease progression and prevent the onset of these difficult-to-treat and potentially life-threatening complications (21–24).

The aim of CHD treatment is to prevent the development of complications of liver disease, such as HCC, cirrhosis, decompensation, requirement for liver transplantation (LT), and death (25). However, at present, the therapeutic options for patients with CHD are limited, and there is no approved treatment for CHD available to patients in the UK (26). NAs, while effective in patients with CHB wherein they are widely used, have not been shown to have a meaningful effect on HDV RNA levels in patients with CHD as they do not inhibit production of HBsAg (the HBV protein required by HDV) (27). Furthermore, IFN-based therapy may be used off-label, but its usage and effectiveness are limited by low treatment eligibility, low response rates, and tolerability concerns, leading to discontinuations, further disease progression, and a significant impact on health-related quality of life (HRQoL) (4,16,28,29). For example, only 25% of patients who receive IFN-based therapy maintain a sustained virologic response after 1 year of treatment (13,30). Overall, IFN-based therapy is estimated to provide a lasting benefit for approximately 10% of patients (16). Given the progressive course of the disease, there is a considerable unmet need for an approved antiviral therapy for the treatment of CHD for patients whose disease has responded inadequately to IFN-based therapy, or who are ineligible to receive IFN-based therapy due to intolerance or contraindication.

Hepatitis delta is recognised as an orphan disease by the European Medicines Agency (EMA), indicating that prevalence is below the threshold of 5 in 10,000 people (7). An estimated 241 HDV-RNA positive patients are treated annually in the UK, of which 152 have evidence of significant fibrosis (METAVIR stage greater than or equal to F2) and have failed, are contraindicated to, or are intolerant of, IFN-based therapy (Figure 2). Clinical experts consulted by Gilead in preparation for this submission confirmed that this figure was broadly accurate and may even be an overestimate of patient numbers (31).

Figure 2: Epidemiological cascade for CHD in the UK



Key: BLV: bulevirtide; HBV: hepatitis B virus; HDV: hepatitis delta virus; IFN: interferon; MA: marketing authorisation; UK: United Kingdom.
[a]Based on British Liver Trust estimates (32).
[b]Based on the estimated proportion of HBV patients co-infected with HDV in the UK population (33).
[c]Based on GSI assumption (34).
[d]Based on exclusions, assuming 9% of diagnosed patients have decompensated cirrhosis, 9% of diagnosed patients have hepatocellular carcinoma, and 2% of patients have required liver transplantation (35).
[e]Based on GSI assumption (34).
[f]Based on assumption that 50% of patients are eligible for IFN-based therapy, of which 25% achieve a sustained response (13,30).
[g]Based on fibrosis stage split in Romeo *et al*. (2009) (35).
Notes: *Non-response defined as failure of, intolerance of, or contraindicated to, IFN-based therapy.

B.1.3.2 Burden of disease

B.1.3.2.1 Clinical burden

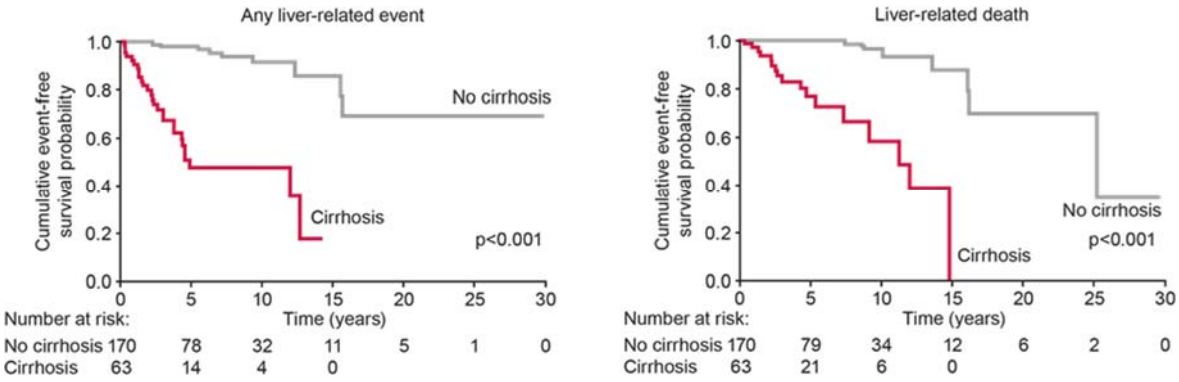
Once a person is infected with HDV, recovery is unlikely, and the chance of this decreases as the disease progresses. Only 10% of patients with CHD experience spontaneous recovery (10). In the early phases of infection, people may experience hepatitis flares, followed by a decrease in HDV replication and subsequent reactivation of HBV (35). For those who do not recover at early stages of the disease, hepatitis delta is associated with an accelerated fibrosis progression, early

liver decompensation with cirrhosis, and increased risk of HCC, leading to greater liver-related mortality compared to HBV or HCV monoinfection (21,22,36).

Persistent viral replication and hepatic inflammation leads to the rapid development of liver cirrhosis in people with hepatitis delta (37). It is expected that 70% of people with hepatitis delta will progress to cirrhosis within 5 - 10 years (18), and 29.7% of those that progress will develop cirrhosis within 3 - 4 years (10). A 2020 retrospective study conducted by Kamal *et al*. (2020), which included 337 people with anti-HDV positivity followed for up to 6.5 years, found that individuals with hepatitis delta and cirrhosis have a greater risk for liver-related events than those without cirrhosis (Figure 3) (38). The likelihood of progressing to cirrhosis is substantially increased in people with CHD, with the majority of these people (53.8%) progressing to cirrhosis within 3 - 4 years (10). The likelihood of progression to cirrhosis is also far greater in people with HDV than in other types of viral hepatitis, such as HCV or HBV monoinfection. For example, 10-20% of people with HCV will develop cirrhosis within 20 years, while for HBV, progression to cirrhosis occurs in 20% of patients within 5 years (39,40).

Following the development of liver cirrhosis, people with CHD may develop symptoms of decompensation, such as ascites, encephalopathy, or variceal bleeding. Compared to those with compensated cirrhosis (CC), patients with decompensated cirrhosis (DCC) have a lower overall rate of survival after 1 year (75% vs 78%) and 5 years (45% vs 67%) (41). LT is often indicated as the only effective therapy option to treat DCC (42). The estimated annual incidence of liver decompensation in people with hepatitis delta and cirrhosis ranges from 2.6% to 3.6% (4). Of note, if HDV is not treated post-transplant, infection of the transplanted liver is likely to occur and can reduce the lifespan of the new liver (43).

Figure 3: Time to event-free survival in participants with and without cirrhosis



Notes: Risk-free survival for composite liver-related outcomes and liver-related death/liver transplantation.
Source: Adapted from Kamal *et al.* (2020) (38).

In addition to an increased risk of cirrhosis and liver decompensation, hepatitis delta is also associated with an increase in the overall risk of HCC compared to people with HBV alone (37,44). Results from a meta-analysis of 93 studies showed that, overall, CHD is associated with a significantly increased risk of HCC compared to HBV monoinfection (44). In addition, HCC commonly occurs against a backdrop of cirrhosis, which is the primary cause of 70-80% of cases (45). In patients with CHD who progress to HCC, progression typically occurs within 10 years (10). Results from Bockmann *et al*. (2020) suggest a high rate (16%) of HCC in 1,127 people with hepatitis delta over three years in Germany (22), while estimates from a study of 200 western European patients suggest a threefold increase in HCC incidence among people with CHD and cirrhosis compared to people with cirrhosis alone (19).

Primary liver cancer represents the eighth most common cause of cancer-related deaths in the UK (46). The main primary liver cancer subtype, HCC, is associated with a high mortality rate, with a median survival following diagnosis of 6 to 20 months (24,47). In the UK, only one third of patients (33.8%) survive to 2 years, with that number reducing to 18.3% at 5 years (47). Currently, the only treatment option for people with HCC due to coinfection or superinfection with HDV and HBV is LT (43,48,49). Compared to people with HBV, people with hepatitis delta require LT more frequently, with 3.44 cases/1,000 person-months versus 0.78 cases/1,000 person-months (50).

The LT procedure, and the associated drugs used to prevent rejection of the donor liver, can cause bleeding, blood clots, infection, mental confusion, seizures and rejection of the donor liver. Furthermore, 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 (51). As such, despite LT offering a treatment option for people with hepatitis delta and end-stage liver disease, it has limitations in terms of accessibility and post-transplant management, highlighting the need for effective treatments at an earlier stage of the disease.

In summary, the rapid progression of disease and development of severe liver complications places a substantial clinical burden on people with CHD (35). As a result, there remains a significant unmet need for an effective treatment at an earlier stage of disease, to prevent downstream consequences. Due to variation in awareness, characteristics of the patient population (see Section B.1.4), limited testing, and issues related to diagnosing techniques, hepatitis delta may have an under-recognised role in the causation of liver-related deaths (33).

B.1.3.2.2 Outcomes for adults with CHD

As highlighted in Section B.1.3.3, the aim of CHD treatment is to prevent the development of complications of liver disease, such as HCC, cirrhosis, decompensation, requirement for LT, and death (25). However, the demonstration of these morbidity- and mortality-related outcomes is not appropriate nor practical for clinical research in hepatitis, as it would require large sample sizes and a prolonged follow-up period. As a result, clinical trials have relied on endpoints such as virological and histological outcomes as surrogate markers, which are likely to predict clinical benefit in people with hepatitis (52).

According to the US Food and Drug Administration (FDA) guidance on developing treatments for CHD, and discussions from the 2019 (European Association for the Study of the Liver) EASL– American Association for the Study of Liver Disease (AASLD) Conference, surrogate endpoints in clinical trials should provide evidence for both a decline in virologic replication, and an improvement in associated liver

inflammation as evidenced by a biochemical response (25,53). The main surrogate endpoint used to predict clinical benefit, as recommended by the FDA, is a combined response, or 'the proportion of trial patients with undetectable serum HDV RNA (defined as undetectable HDV RNA [HDV RNA <LoD, where LoD=6 IU/mL] or decrease in HDV RNA by ≥2-$\log_{10}$ IU/mL from baseline) and alanine aminotransferase (ALT) normalisation' (53).

Increases in HDV RNA levels are associated with increased infectivity, progression of disease, and development of long-term complications (20). High HDV RNA levels are correlated with disease activity and have been shown to be associated with disease progression to cirrhosis and an increased risk of HCC (35). In a study by Braga *et al*. (2014), HDV RNA levels were shown to positively correlated with neuroinflammatory activity and fibrosis stage, with advanced fibrosis being associated with an HDV viral load ≥2-$\log_{10}$ (54). In a 2009 Italian study by Romeo *et al*., which analysed data from participants who had been HDV positive for at least six months, HDV viraemia was found to be the strongest predictor of cirrhosis, liver decompensation, HCC and death (35). Roulot *et al*. (2020) found that detectable HDV RNA is associated with decompensation (36). Results from the same study indicate a trend for increased levels of HDV viraemia in individuals with cirrhosis but without complications compared to those with clinical decompensation and HCC (36). Similarly, results from a study by Yamashiro *et al*. (2004) suggest that levels of HDV RNA were significantly higher in people with CHD and cirrhosis compared to asymptomatic carriers (55). These results suggest that HDV RNA may be related to progression to CHD, and therefore a reduction in HDV RNA levels is a highly relevant endpoint to predict a clinical benefit in people with CHD (56).

Similar to a reduction in HDV RNA replication, a biochemical response (defined as normalisation of ALT based on the upper limit of normal [ULN]) is also suggested to predict long-term clinical benefit in people with CHD. ALT is a liver enzyme that indicates ongoing inflammation or injury to liver cells as it is released into the blood as hepatocytes die. It is a general (not specific to HDV infection) marker of current liver damage. Elevated ALT has been associated with long-term complication such as cirrhosis and HCC (57). Sustained reduction in ALT, as observed in patients

receiving effective therapy for HBV monoinfection (58,59), correlates with improved long-term liver-related outcomes, including reduction in cirrhosis and HCC (60).

The use of ALT normalisation has been included in multiple Phase 3 clinical trials in viral hepatitis as an indicator of efficacy. In a community-based prospective cohort study by Chen *et al*. (2011), which included 23,820 participants with CHB, it was indicated that the cumulative lifetime risk of developing cirrhosis increased in correlation with higher ALT levels. Likewise, the study presented evidence that the cumulative lifetime risk of developing HCC increased with higher levels of ALT (61). Furthermore, in a study by Zachou *et al*. (2010), which included 80 subjects with CHD, elevated ALT serum levels were associated with the development of fibrosis (62).

Given the association of ALT and disease progression in viral hepatitis, the normalisation of ALT is also shown to correlate with an improvement in morbidity (63). A study by Choi *et al*. (2020), which included 4,639 participants with CHB who initiated treatment with entecavir or tenofovir (TDF), found that ALT normalisation was independently associated with a proportionally lower risk of HCC, regardless of fatty liver or cirrhosis at baseline and while on treatment (64). Furthermore, the association of ALT and risk of hepatic events is further evidenced by Wong *et al*., (2018), who found that participants with normalised ALT at 3, 6, 9, and 12 months of treatment had a reduced risk of hepatic events compared to participants without normalised ALT (65). However, clinical expert feedback highlighted that a decline in HDV RNA and ALT normalisation may not always occur in parallel, and therefore ALT normalisation can be viewed as a lagging indicator of treatment response (31).

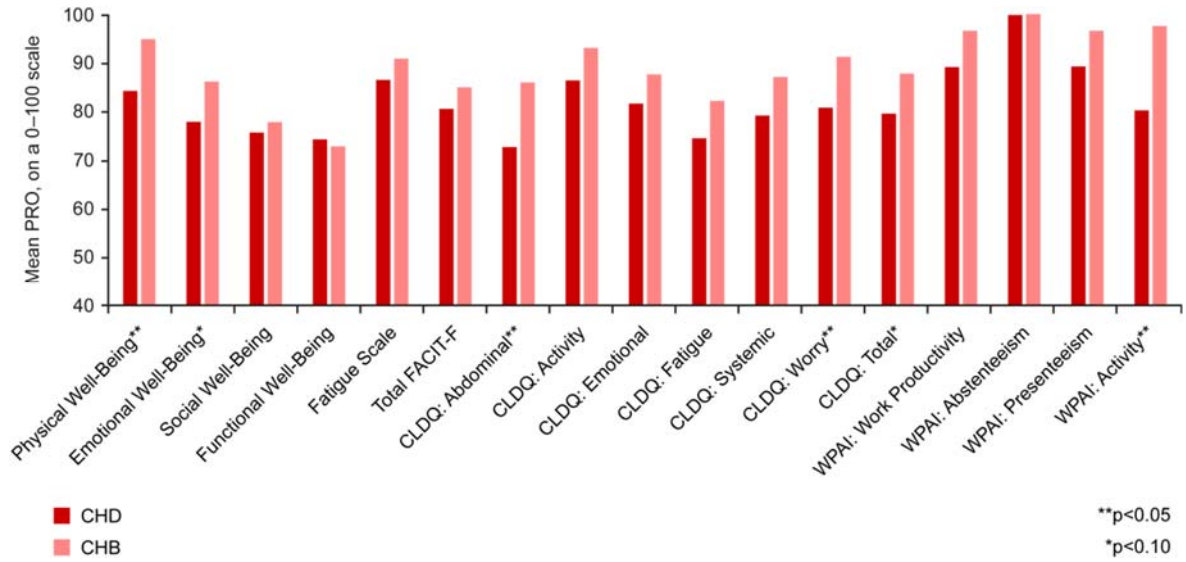
B.1.3.2.3 Humanistic burden

In addition to the substantial clinical burden, people infected with hepatitis delta may suffer from negative effects on quality of life (QoL) (66–68). A 2017 German retrospective study by Stahmeyer *et al*. investigated QoL, using the EuroQoL-5 Dimension (EQ-5D) time trade-off method and Visual Analogue Scale (VAS) method (where score of 1 refers to perfect health and a score of 0 refers to death), in 117 participants with HBV, of which 16 participants were coinfected with HDV. Of the

participants with hepatitis delta, QoL scores were approximately 0.81 and 0.64 for EQ-5D and VAS, respectively (67). The same study also found that people with hepatitis delta experience a restriction in QoL due to the disease, with 52% of people reporting moderate, severe, or very severe restriction in QoL (67). Treatment of hepatitis delta has also been found to impact QoL, with depression a common side-effect of PEG-IFN treatment. A study conducted in Turkey by Dagli *et al*. (2018) reported high scores of depression in all participants with hepatitis delta (n=28), during and at the end of PEG-IFN treatment (66).

In a single-centre study by Buti *et al*. (2021) examining patient reported outcome (PRO) scores in people with CHD receiving NA therapy, people coinfected with hepatitis delta experienced more impairment in PRO scores compared to population norms, reporting more severe abdominal symptoms and more impairment in their daily activities (Figure 4) (66). PRO scores range from 0-100, where higher scores indicate a better QoL.

Figure 4: PROs in people with CHD versus CHB



Key: CHB: chronic hepatis B; CHD: chronic hepatitis delta; CLDQ: Chronic Liver Disease Questionnaire; FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue; PRO: patient-reported outcome; WPAI: Work Productivity and Activity Impairment.
Notes: all parameters were normalised to a scale of 0–100. T-student test and Mann-Whitney U-test were used for parametric and non-parametric categories, respectively. P-values of 0.05 or less were considered statistically significant. *p<0.10; **p<0.05.
Source: Adapted from Buti *et al*. (2021) (66).

B.1.3.2.4 Economic and societal burden

The cost of living with hepatitis delta is currently based on evidence from the US. People with hepatitis delta experience a significantly higher health care resource utilisation (HCRU) and cost burden (69). In addition, people with hepatitis delta incurred significantly higher total annual health care service costs of $23,605 per individual, compared to $18,228 for people with HBV alone (69). The economic burden associated with hepatitis delta is also driven by disease severity, with an increase in healthcare costs associated with hepatitis delta increase as the disease progresses (70).

Furthermore, hepatitis delta is associated with indirect costs related to lost productivity of people due to work absenteeism. Loss of work productivity related to hepatitis delta and treatment is estimated at $14, $180, and $506 in 2010 over one year for people CC, DCC, and HCC, per person, respectively (70).

B.1.3.3 Clinical care pathway

Treatment guidelines for HDV are used to inform the most appropriate management of people with CHD. Current guidance for HDV patient management in Europe, issued by EASL, is limited to a sub-section within the clinical guidelines for the management of HBV infection (27). In the US, AASLD has published a standalone guideline for the diagnosis and management of people with CHD (71). Whilst NICE do not provide full guidelines on the treatment of chronic HDV - potentially due to the orphan nature of the disease and lack of approved treatment options - they do provide recommendations for drug treatment in adults with HBV-HDV co-infection (72).

B.1.3.3.1 EASL guidelines

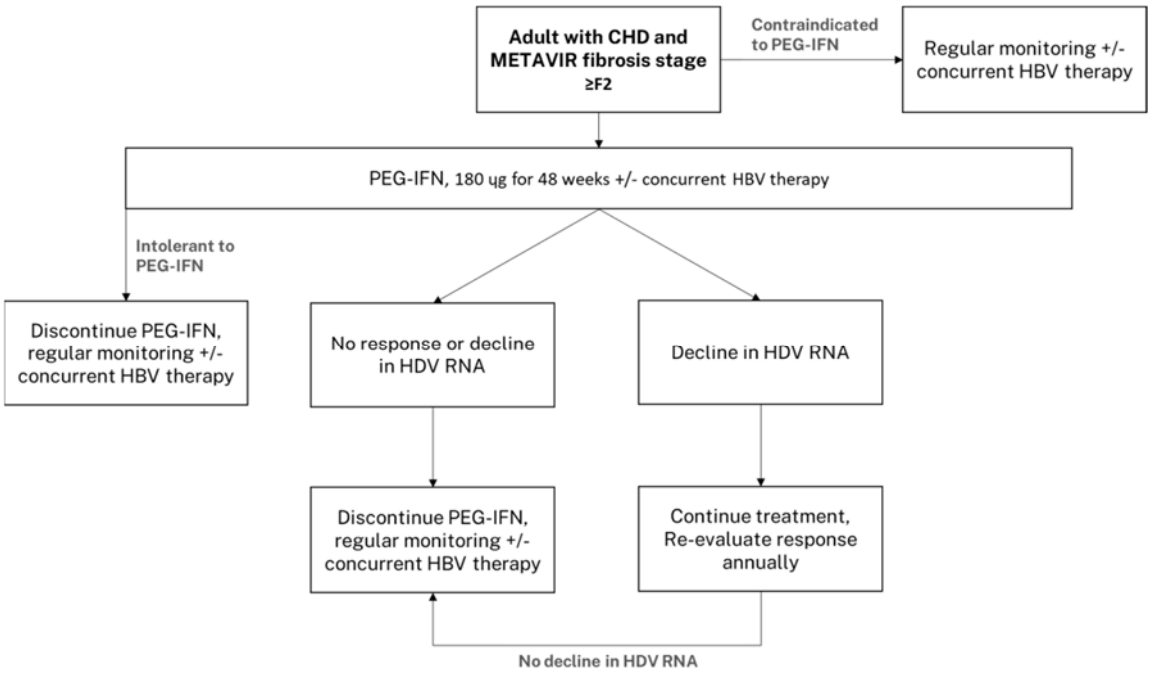
The EASL guidelines strongly recommend treatment with PEG-IFN for at least 48 weeks in HDV-HBV coinfected patients with compensated liver disease, irrespective of on-treatment response pattern if well-tolerated, illustrating the paucity of treatment options available for these patients. NA therapy, which has no activity against HDV but is highly effective in inhibiting HBV, is recommended in HDV-HBV co-infected patients with ongoing HBV DNA replication (27).

B.1.3.3.2 NICE guidelines

The NICE treatment pathway for adults with CHB provides recommendations for the diagnosis and antiviral treatment of CHD (Figure 5).

NICE clinical guideline CG165 for the diagnosis and management of CHB stipulates that adults who are HBsAg positive should be tested for anti-HDV (72). Those confirmed as having been exposed to HDV must then be tested for current infection using a HDV RNA PCR test. Adult patients co-infected with CHB and hepatitis delta infection, who have evidence of significant fibrosis (METAVIR fibrosis stage greater than or equal to F2 or Ishak stage greater than or equal to 3), should be offered a 48-week course of PEG-IFN (72). The use of PEG-IFN is off-label as treatment of patients infected with HDV is not within the marketing authorisation (73), In addition, the technology appraisal guidance [TA96] does not apply to adults with CHB known to be co-infected with hepatitis delta (74). Treatment with PEG-IFN should be stopped if there is no decrease in HDV RNA after 6 months to 1 year of treatment. Otherwise, treatment should be continued with response evaluated annually (72).

Figure 5: Treatment algorithm for adult CHD



Key: CHD: chronic hepatitis delta; HBV: hepatitis B virus; HDV: hepatitis delta virus; RNA: ribonucleic acid; PEG-IFN: peginterferon-alpha-2a.
Source: Adapted from NICE clinical guidance CG165 for hepatitis B (72).

B.1.3.3.3 Unmet needs with current treatment

National and international guidelines for hepatitis delta are limited to recommending off-label PEG-IFN (27,72). EASL guidelines recommend 48 weeks of treatment with PEG-IFN, irrespective of response pattern if well tolerated, illustrating the paucity of available treatment options to patients with CHD (27). A study by Romeo *et al*. (2009) found that 58.7% of patients at enrolment had received no treatment for CHD, while only 39.1% received treatment with IFN-based therapy over a period of 233 months (35), further highlighting the absence of effective therapeutic options.

There is some evidence to suggest that off-label treatment with IFN-based therapy may result 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, however the evidence is limited (20).A substantial portion (~50%) of patients are ineligible for IFN-based therapy, due to contraindications, intolerabilities, or advanced liver disease (36). In addition, of those who do receive treatment, only 25% achieve a sustained response, and approximately 50% of these individuals relapse (13,30). Taking these factors into consideration, IFN-based therapy is estimated to provide a lasting benefit for only 10% of CHD patients (16).

In the absence of off-label IFN-based therapy, the only treatment option for patients with CHD is BSC, generally defined as symptomatic treatment as well as treatment for the underlying CHB where indicated. Treatments for HBV, such as NAs, demonstrate no efficacy against CHD because the replication of HDV is completely autonomous from that of HBV (4). HDV only requires the envelope glycoprotein HBsAg from HBV. Thus, whilst HBV-specific treatments such as NAs strongly suppress HBV replication, they have no effect on HDV replication and little effect on HBsAg production (4).

As a reflection of the above, experts consulted during the development of the European Public Assessment Report (EPAR) agreed that there is an unmet medical need for bulevirtide, and that chronic HDV infected, or HDV-RNA positive adult patients with compensated liver cirrhosis, would constitute a patient population in

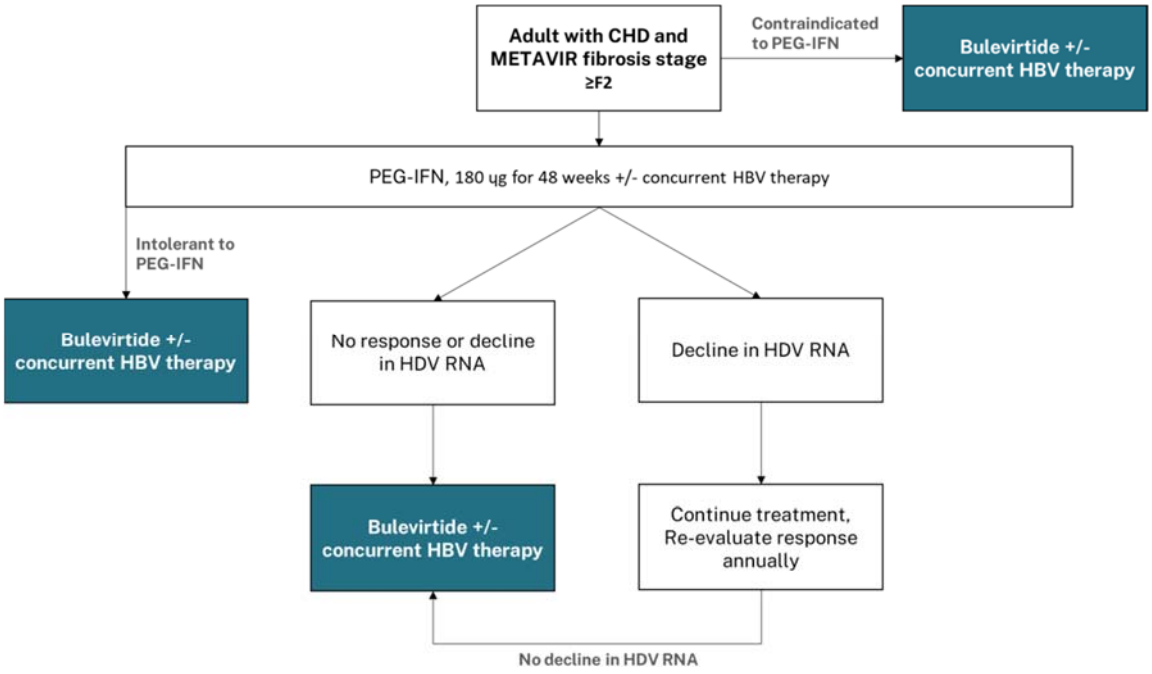
urgent need of treatment with bulevirtide , thus supporting a conditional approval to provide timely access (3).

B.1.3.3.4 Proposed positioning of bulevirtide in the adult CHD pathway

Bulevirtide is a novel, first-in-disease and first-in-class entry inhibitor, and the only approved treatment for CHD. Bulevirtide is positioned as a treatment option for adults with CHD who have compensated liver disease, and evidence of significant fibrosis (METAVIR stage greater than or equal to F2), whose disease has responded inadequately to IFN-based therapy, or who are ineligible to receive IFN-based therapy due to intolerance or contraindication.

The proposed positioning of bulevirtide is displayed schematically in Figure 6.

Figure 6: Proposed positioning of bulevirtide in the adult CHD treatment pathway



Key: CHD: chronic hepatitis delta; HBV: hepatitis B virus; HDV: hepatitis delta virus; RNA: ribonucleic acid; PEG-IFN: peginterferon-alpha-2a.

There are currently no approved treatments available in the UK for the treatment of CHD, and off-label treatment with IFN-based therapy is associated with limited efficacy and an unfavourable safety profile, with only 10% of patients experiencing a

lasting benefit as a result of treatment (16). The limitations of current off-label treatment with IFN-based therapy, as described in Section B.1.3.3.3, present a significant unmet need for an effective treatment for hepatitis delta to reduce morbidity and side-effects among patients whose disease has responded inadequately to IFN-based therapy, or who are ineligible to receive IFN-based therapy due to intolerance or contraindication.

Therefore, the availability of a treatment for these patients would provide a valuable addition to the treatment armamentarium. The following text provides more detail on the unmet need that exists in the proposed positioning of bulevirtide.

Adults with CHD: inadequate response to IFN-based therapy

In clinical trials, only 25% of patients demonstrate a sustained response to IFN-based therapy, and approximately 50% of these individuals will eventually relapse once treatment with IFN-based therapy is completed, giving an overall response rate of 10% (13,30). In the post-hoc analysis of the HIDIT-II study, which included people with HBV and HDV, Bremer *et al*. (2021) found that HDV relapses occurred in 67% of individuals with detectable low HDV RNA after PEG-IFN treatment at Week 48, and in 77% of people who had undetectable HDV RNA after PEG-IFN treatment at Week 96 (75).

Adults with CHD: intolerant of IFN-based therapy

Treatment of hepatitis delta with IFN-based therapy is associated with significant toxicity (29). Adverse events (AEs) as a result of treatment are frequent and severe, which resulted in 20% of patients withdrawing prematurely from therapy in the HIDIT-II trial (76). Unwanted side-effects caused by treatment with IFN-based therapy include flu-like symptoms, myalgias, arthralgias, exacerbation of psychiatric illnesses, haematologic toxicity, and elevation of transaminases (20). These have the potential to lead to treatment discontinuation and low treatment compliance. Many side-effects can only be managed through dose adjustment or the cessation of treatment (29).

Adults with CHD: ineligible for treatment with IFN-based therapy

Additionally, clinical experience indicates that only 50% of patients are eligible for therapy with IFN-based therapy, due to contraindications, intolerabilities or advanced liver disease (36). As a result, many patients do not initiate treatment. In an Italian study analysing 299 patients with HDV followed-up over a mean period of 233 months, only 39.1% of patients received treatment with IFN-based therapy (35).

B.1.4 Equality considerations

Clinical experts consulted by Gilead raised several issues with regards to equality, including language barriers and patient voice (31). A retrospective study of HDV co-infection in South London found the prevalence of anti-HDV in ~1,000 carriers of HBsAg with chronic liver disease was 8.5%, with 28.1% the HDV-infected subjects born in southern or eastern Europe, 26.8% born in Africa, and 7.3% born in central Asia (77). Due to the implementation of HBV vaccination programmes, the incidence of HDV has significantly decreased in Europe. However, due to increased migration of people from highly endemic areas, this decline has recently been reversed (78). A pattern of increasing migrant HDV infections and a decline in native HDV infections in Europe has resulted in a dual epidemiology of hepatitis delta: an aging domestic cohort with advanced liver fibrosis, representing the end stage of the natural history, and a younger generation of foreign born patients who account for the majority of new infections (28).

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify the clinical evidence relevant to the technology being appraised.

See Appendix D1.3 for full details of the process and methods used to identify and select the clinical evidence relevant to bulevirtide for the treatment of adults with CHD who have compensated liver disease.

B.2.2 List of relevant clinical effectiveness evidence

Five trials were identified in the clinical SLR that provide direct clinical evidence for the efficacy and safety of bulevirtide for the treatment of adults with CHD. Table 3 provides justification for the bulevirtide studies considered relevant to this submission, and those that will not be described in this section. A description of the studies providing relevant clinical effectiveness evidence can be found in Table 77 (Appendix D1.3).

Table 3: Studies investigating the efficacy and safety of bulevirtide

Study name	Linked Publications	Rationale
Studies presented in the submission		
MYR 301 (Wedemeyer *et al.* 2021 (79)	Allweiss *et al*. 2021 (80); Wedemeyer *et al* 2021 (81)	Pivotal Phase 3 study analysing the efficacy and safety of bulevirtide versus a delayed treatment arm.
MYR 202 (Wedemeyer *et al.* 2018 (82)	Allweiss *et al*. 2018 (83); Allweiss *et al*. 2019 (84); Wedemeyer *et al*. 2017 (85)	Comparison versus NAs (BSC) within the scope of the decision problem
Studies not presented in the submission		
MYR 201 (Bogomolov *et al*. 2016) (86)	Bogomolov *et al*. 2016 (87)	Comparison versus PEG-IFN outside of the scope of decision problem, endpoints not relevant, and population not relevant
MYR 203 (Wedemeyer *et* al 2019) (88)	Wedemeyer *et al*. 2018 (89); Wedemeyer *et al.* 2020 (90); Wedemeyer *et al*. 2019 (91); Wedemeyer *et al*. 2020 (92)	Comparison versus PEG-IFN outside the scope of decision problem

MYR 204	Asselah *et al*. 2021 (93)	Endpoint (sustained virologic response) not relevant to indication, study evaluating bulevirtide + PEG-IFN vs IFN alone

Key: BSC: best supportive care; IFN: interferon; NA: nucleos(t)ide analogue; PEG-IFN: peginterferon-alpha-2a.

One Phase 3 trial (MYR 301) and one supportive Phase 2 trial (MYR 202) were identified in the clinical SLR that provide direct clinical evidence for the efficacy and safety of bulevirtide for the treatment of adult subjects with CHD against BSC. The pivotal MYR 301 multicentre, open-label, Phase 3 clinical trial evaluating the efficacy and safety of bulevirtide compared to BSC in adults with CHD is ongoing. Therefore, the primary source of data underpinning this submission is available from the MYR 301 interim week 48 clinical study report (CSR), dated January 2022 (59). To date, two conference abstracts relating to interim data are available in the public domain (79,81), with additional interim data expected to be published at the EASL International Liver Congress, 22-26 June 2022 (94).

Supporting clinical evidence of the efficacy and safety of bulevirtide for the treatment of CHD is available from the MYR 202 Phase 2 trial. The SLR identified three publications relating to MYR 202 in the public domain (82,83,85). Results from MYR 202 have also been presented in the EMA EPAR (95).

Interim data at 24 weeks for MYR 301 was published in the *Journal of Hepatology* (79), while an exploratory analysis focusing on PROs was published in *Hepatology* (81). Results from MYR 202 were presented in the *Journal of Hepatology* (82–85). Where possible, information will be sourced from the public domain.

Patients enrolled in MYR 301 will be treated for 144 weeks with bulevirtide, before a follow-up period of 96 weeks to assess off-treatment response (i.e., a total of 240 weeks). Table 4 and Table 5 present a summary of the relevant clinical effectiveness evidence for bulevirtide.

Table 4: Clinical effectiveness evidence: MYR 301

Study	MYR 301 (NCT03852719)
Study design	A multicentre, open-label, randomised Phase 3 clinical study to assess the efficacy and safety of bulevirtide
Population	Adults with CHD
Intervention(s)	Bulevirtide
Comparator(s)	Delayed treatment
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	MYR 301 presents the pivotal, regulatory, clinical evidence in support of bulevirtide for the treatment of CHD.
Reported outcomes specified in the decision problem	• **Virological response** • **Biochemical response** • Mortality • **Adverse effects of treatment** • **Health-related quality of life**
All other reported outcomes	• Liver-related clinical events

Key: CHD: chronic hepatitis delta; HDV: hepatitis delta virus.
Notes: outcomes in bold are those directly used in the economic modelling.

Table 5: Clinical effectiveness evidence: MYR 202

Study	MYR 202 (NCT03546621)
Study design	A Phase 2, randomised, open-labelled, multicentre clinical study to assess the efficacy and safety of 3 doses of bulevirtide
Population	Adults with CHD
Intervention(s)	Bulevirtide + TDF
Comparator(s)	TDF
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	No
Rationale if study not used in model	Clinical efficacy of bulevirtide will be informed by the results of the pivotal Phase 3 MYR 301 study.
Reported outcomes specified in the decision problem	• Virological response • Biochemical response • Mortality • Adverse effects of treatment
All other reported outcomes	Not applicable

Key: ALT: alanine aminotransferase; CHD: chronic hepatitis delta; TDF: tenofovir.

MYR 202 studied patients with CHD and quantifiable HDV virus replication, including a proportion for whom previous treatment with IFN-based therapy failed or who were considered IFN-based therapy intolerant, as well as patients with compensated cirrhosis. Bulevirtide was compared against TDF alone, a treatment for the underlying hepatitis B. This comparator is aligned to the comparator in this submission, of BSC. In addition, the sub-population of patients who had failed or were intolerant to IFN-based therapy aligns to the population proposed in the decision problem. Therefore, despite data from MYR 202 not being used to populate the economic model, the study provides an additional source of supporting evidence and is included in Sections B.2.2 to B.2.6.

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 MYR 301

B.2.3.1.1 Trial methodology

Table 6: Summary of trial methodology for MYR 301

Trial Number (Acronym)	NCT03852719 (MYR 301)
Location	The study is being conducted at 16 sites across four countries globally. These countries are Russia (7 sites), Germany (5 sites) Italy (3 sites) and Sweden (1 site).
Trial design	A multicentre, open-label, randomised Phase 3 clinical study to assess efficacy and safety of bulevirtide in patients with CHD.
Eligibility criteria for participants	Male and female patients with CHD (≥6 months prior to screening) aged 18-65 years with or without liver cirrhosis, who had: • Elevated ALT levels (>1 x ULN), but <10 x ULN) • Child-Pugh score of ≤7 points • Serum albumin >28 g/L • Creatine clearance ≥60 mL/min (Cockcroft-Gault formula) • Total bilirubin <34.2 µmol/L at screening. • Subjects with current or previous (within the past 2 years) decompensated liver disease were excluded • Subjects with controlled human immunodeficiency virus (HIV) were allowed.
Settings and locations where the data were collected	Treatment and all study procedures were performed on an outpatient basis (except for hospitalisation for biopsy procedure, if required).
Study periods and trial drugs	Eligible patients were randomly assigned to three treatment groups (randomisation ratio 1:1:1:) stratified by the presence of liver cirrhosis: • **Group A**: delayed treatment with BLV 10 mg/day for 96 weeks after an observational period of 48 weeks. • **Group B**: immediate treatment with BLV 2 mg/day for 144 weeks. • **Group C**: immediate treatment with BLV 10 mg/day for 144 weeks. The interim readout describes the study results when all participants had completed the Week 48 visit. A total of 8 study visits were made during this period.

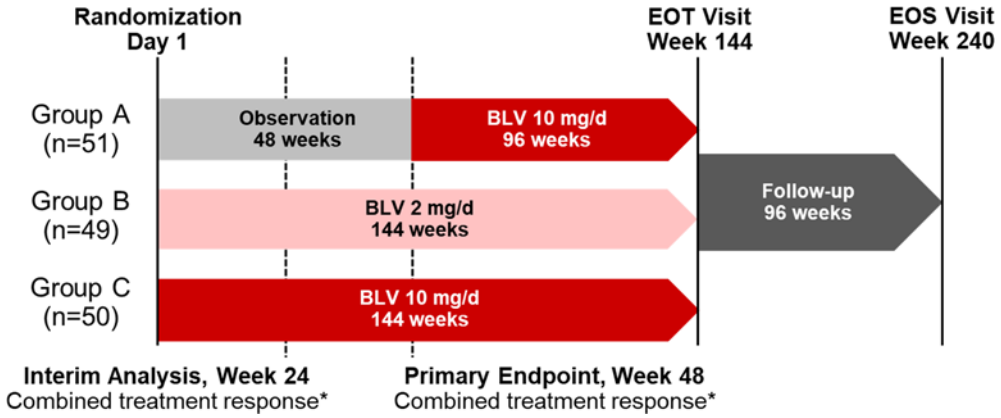
Prior and concomitant Medication	• Subjects who had ongoing treatment with NAs for CHB were allowed to continue their treatment as prescribed on screening and during study participation. • For subjects with no ongoing treatment with NAs for CHB, treatment was initiated at the baseline visit or later in the study if indicated, in accordance with the current EASL/AASLD treatment guidelines.
Primary outcome	Combined response at Week 48, defined as the fulfilment of both of the following: • Undetectable (< LoD) HDV RNA or decrease by ≥2-$\log_{10}$ IU/mL from baseline • ALT normalisation
Secondary outcomes used in the model/ specified in the scope	• Undetectable HDV RNA at Week 48 • HDV RNA decrease by ≥2-$\log_{10}$ IU/mL from baseline at Week 48. • ALT normalisation at Week 48 • EQ-5D data at baseline and all post-baseline assessments
Pre-planned subgroups	• Patients with liver cirrhosis • Patient without liver cirrhosis

Key: AASLD: American Association for the Study of Liver Diseases; ALT: alanine aminotransferase; BLV: bulevirtide; CHB: chronic hepatitis B; CHD: chronic hepatitis delta; CSR: clinical study report; EASL: European Association for the Study of the Liver; EQ-5D: EuroQol (5 dimensions [EQ-5D-3L]); HDV: hepatitis delta virus; HIV: human immunodeficiency virus; LoD: law of detection; NA: nucleos(t)ide analogue; PCR: polymerase chain reaction; RNA: ribonucleic acid; ULN: upper limit of normal.
Source: MYR 301 CSR (59).

B.2.3.1.2 Trial design

MYR 301 is an ongoing Phase 3 multicentre, open label, randomised clinical study evaluating the efficacy and safety of bulevirtide treatment (2 mg and 10 mg) in people with CHD, in comparison to delayed treatment. The dose regimen approved by the MHRA and under review in this submission, is bulevirtide 2 mg (8). The study design for MYR 301 is depicted in Figure 7.

Figure 7: MYR 301 study design and dosing



Key: BLV: bulevirtide; EOS: end of study; EOT: end of treatment; mg/d: milligrams per day.
Notes: *Combined response is defined as undetectable HDV RNA or a ≥2-$\log_{10}$ IU/mL decline from baseline and ALT normalisation.
Source: MYR 301 CSR (59).

Approximately 150 adult subjects with CHD were to be assessed to evaluate the efficacy and safety of bulevirtide, with the proportion of responders achieving a combined response after 48 weeks as the primary endpoint. A combined response was defined as the fulfilment of both of the following:

- Undetectable (< LoD) HDV RNA or decrease by ≥2-$\log_{10}$ IU/mL from baseline at Week 48
- ALT normalisation (ALT ≤ ULN regardless of baseline ALT level) at Week 48

Of note, ALT normalisation at Week 48 was defined as an ALT value within normal range as defined by each central lab based on their standard procedures. Normal ALT was defined as ≤ 31 U/L for females and ≤ 41 U/L for males for study sites in Russia. For all other sites, the normal ALT range was ≤ 34 U/L for females and ≤ 49 U/L for males (59).

Participants were randomly assigned to a treatment group in a 1:1:1 ratio, by means of an electronic randomization system, with stratification for the presence of liver cirrhosis. The three groups are described below:

- **Group A**: bulevirtide 10 mg/day for 96 weeks after an observational period of 48 weeks
- **Group B**: bulevirtide 2 mg/day for 144 weeks

- **Group C**: bulevirtide 10 mg/day for 144 weeks

Last observation carried forward (LOCF) was used to impute missing values for the combined response if the missing value was related to COVID-19; otherwise, a missing equals failure approach was employed i.e., participants with a missing value were considered as non-responders. Subjects in the delayed bulevirtide arm received no treatment for hepatitis delta for the initial 48 weeks of the study in the observational period. Participants who had ongoing treatment with NAs for CHB were allowed to continue their treatment as prescribed in screening and during study participation. For participants with no ongoing treatment with NAs for CHB, treatment was to be initiated at the baseline visit or later if indicated, in accordance with the current EASL/AASLD guidelines (72,96). At Week 48, participants in the delayed bulevirtide arm were to be switched to bulevirtide 10 mg for 96 weeks (144 weeks of treatment in total). After Week 144, a follow-up period of 96 weeks (off-treatment) was also included for all treatment groups i.e., a total of 240 weeks (59).

The selection of doses in MYR 301 was based on results obtained at Week 24 in the MYR 202 study (59).

B.2.3.1.3 Eligibility criteria

The key inclusion and exclusion criteria for MYR 301 are described in Table 7.

Table 7: Key eligibility criteria for MYR 301

Key Inclusion Criteria	Key Exclusion Criteria
• People aged 18-65 years. • Positive serum anti-HDV antibody result or PCR result for serum/plasma HDV RNA for at least 6 months before screening. • Positive PCR results for serum/plasma HDV RNA at screening. • ALT level >1 x ULN, but < 10 x ULN. • Serum albumin >2.8 mg/dL.	• Child-Pugh score of > 7 points. • HCV or uncontrolled HIV coinfection. • Creatinine clearance < 60 mL/min as estimated using Cockcroft-Gault formula. • Total bilirubin ≥34.2 µmol/L. • Evidence of an active or suspected malignancy or a history of malignancy, or an untreated pre-malignancy disorder within the last 5 years.

	• Current or previous (within last 2 years) decompensated liver disease, including coagulopathy, hepatic encephalopathy, and oesophageal varices haemorrhage. • Use of IFN within 6 months before screening. • Receipt of bulevirtide previously, eg, in clinical studies.

Key: ALT: alanine aminotransferase; HCV: hepatitis C virus; HDV: hepatitis delta virus; HIV: human immunodeficiency virus; IFN: interferon; PCR: polymerase chain reaction; ULN: upper limit of normal.
Source: Section 7.2, MYR 301 CSR (59).

For a full list of eligibility criteria please refer to the CSR (59).

Prospective participants were screened within 28 days before the baseline visit (day 1) to determine eligibility for participation in the study. Eligibility was determined by the following assessments:

- Inclusion/exclusion criteria
- Medical history
- Prior and concomitant therapy
- Weight, height, body mass index (BMI)
- Physical examination
- Vital signs include body temperature, heart rate, and blood pressure.
- 12-lead electrocardiogram (ECG)
- Abdominal ultrasound
- Transient elastometry (FibroScan®)
- Breath alcohol test
- Liver biopsy

Liver biopsy had to be performed within ± 7 days from the date of the visit for participants who did not have medical contraindications for the procedure. If baseline liver biopsy samples were not available (were not provided to central laboratory or were considered as non-evaluable by central laboratory), subsequent liver biopsy was not to be performed.

B.2.3.1.4 Settings and locations where the data were collected

Subjects were randomised and treated with bulevirtide at 16 study sites: seven in Russia, five in Germany, three in Italy, and one in Sweden. Treatment and all study procedures were performed on an outpatient basis (except for hospitalisation for biopsy procedure, if required). Central laboratories were blinded to actual treatment allocation.

B.2.3.1.5 Trial drugs and concomitant medications

Bulevirtide

In MYR 301, the study drug was bulevirtide. This was provided as a lyophilised powder for single use in sterile vials of 5.0 or 2.0 mg/vial. The product was reconstituted in 1 ml water for injection prior to administration. The dosages of bulevirtide used in the study were 2 mg or 10 mg according to the treatment group randomly assigned. Participants randomised to the bulevirtide 10 mg treatment group were required to receive two injections of bulevirtide 5 mg daily for this dose level, compared with one injection daily for the bulevirtide 2 mg treatment group. Dose adjustments were not allowed in the study. Bulevirtide was administered by subjects at home, or by the healthcare professional at the site when the subject was attending a study centre visit.

Concomitant medication

Patients who received treatment with TDF or entecavir for chronic HBV infection were allowed to continue treatment as prescribed on screening and during study participation. Treatment with TDF or entecavir was provided to previously untreated patients with chronic HBV infection, if indicated in accordance with the current

EASL/AASLD treatment guidelines (27,96), at a baseline visit or later in the study. Treatment with an NA was initiated if one of the following conditions was met:

- HBV DNA >2,000 IU/mL and ALT >ULN, or HBV DNA >2,000 IU/mL and at least moderate necroinflammation or fibrosis, or HBV DNA >2,000 IU/mL and ALT >ULN and at least moderate necroinflammation or fibrosis
- Liver cirrhosis with any detectable HBV DNA level
- Patients with HBV DNA >20,000 IU/ml and ALT >2x ULN should start treatment regardless of the degree of fibrosis
- Family history of cirrhosis or HCC
- Presence of extrahepatic manifestations

In patients in whom TDF was contraindicated, entecavir (tablets) was provided.

Restricted medication

Restricted medications included systemic glucocorticosteroids, immunomodulatory agents, and antiviral drugs for HBV and/or HDV treatment (apart from allowed NAs). For the full list of restricted medications, please see the CSR (58).

B.2.3.1.6 Outcomes used in the economic model or specified in the scope, including primary outcome

The primary efficacy endpoint to evaluate the efficacy of bulevirtide was the proportion of subjects achieving a combined response at Week 48. Combined response was defined as fulfilment of the following:

- Undetectable (< LoD) HDV RNA or decrease by ≥2-$\log_{10}$ IU/mL from baseline at Week 48
- ALT normalisation (ALT ≤ ULN regardless of baseline ALT level) at Week 48

As highlighted in Section B.1.3.2.2, a combined response was recommended by the FDA as the key surrogate endpoint able to provide evidence for both a decline in

virologic replication, and an improvement in associated liver inflammation evident by a biochemical response (53).

Other secondary efficacy endpoints used to evaluate the optimal treatment duration of bulevirtide include:

- HDV RNA decrease by ≥2-$\log_{10}$ IU/mL from baseline to Week 48
- HDV RNA decrease by ≥2-$\log_{10}$ IU/mL or undetectable HDV RNA at Week 48
- Undetectable HDV RNA at Week 48
- ALT normalisation at Week 48
- Change from baseline in liver stiffness and histological activity at Week 48

The proportion of subjects with a sustained virologic response (defined as undetectable HDV RNA recorded at 24 weeks and 48 weeks after the scheduled end of treatment) will be assessed at study weeks 168 and 192 and therefore is not described in this submission.

Quality of life captured by the European Quality of Life 5 Dimensions 3 Level (EQ-5D-3L) quality of life scale was an additional exploratory endpoint. However, as elaborated in Section B.2.6.1.2, the baseline EQ-5D-3L scores observed in MYR 301 were not affected by cirrhotic status. As such, the face validity of EQ-5D-3L data collected during MYR 301 may be questioned; further discussion around the EQ-5D-3L data is provided in Section B.2.12.1.

Safety evaluations used to assess the safety of bulevirtide monitored the frequency and nature of AEs, based on the assessment of clinical events, physical examination, vital signs, ECG, and laboratory tests. Changes in vital signs, heart rate, and laboratory tests (haematology, coagulogram, biochemistry, blood bile salts, vitamin D) were all assessed.

B.2.3.1.7 Patient datasets and baseline characteristics

Efficacy analyses were performed using the full analysis set (FAS), unless otherwise specified. The FAS comprised all participants either randomised to the delayed treatment group, or randomised to bulevirtide and who received bulevirtide at least once after randomisation. The safety population was the same as the FAS and is defined as all randomised patients who received at least one dose of bulevirtide (59). Safety data were analysed by treatment group according to the actual treatment received (not the randomised treatment).

It is worth noting that in MYR 301, a total of [redacted] were excluded from the Week 48 per protocol analysis set (PPAS). [redacted] were excluded from analysis in the delayed treatment arm, as [redacted] had their visit for the primary endpoint (Week 48) performed outside the protocol-specified window (>14 days) and [redacted] withdrew from the study due to pregnancy. Of the [redacted] in the bulevirtide 2 mg treatment group excluded from the PPAS, [redacted] had major protocol deviation where the study drug was administered incorrectly (categorised as a missed dose), and [redacted] was withdrawn before Week 48 due to withdrawal of consent. Finally, [redacted] in the bulevirtide 10 mg treatment group were excluded from the PPAS due to withdrawal of consent ([redacted]), physician decision ([redacted]), and the observation of a major protocol deviation where the assessment procedure was not performed (59).

A summary of the analysis sets is provided in Table 8.

Table 8: Summary of MYR 301 datasets

Analysis Set, (n, %)	Delayed Treatment (n=51)	BLV 2mg (n=49)	BLV 10mg (n=50)	Total (n=150)
Randomised Set	51	49	50	150
Safety Analysis Set	[redacted]	[redacted]	[redacted]	[redacted]
Full Analysis Set	[redacted]	[redacted]	[redacted]	[redacted]
Per Protocol Analysis Set	[redacted]	[redacted]	[redacted]	[redacted]

Key: BLV: bulevirtide.
Notes: Percentages were based on the number of subjects within each treatment group.
Source: Table 11, MYR 301 CSR (59).

Table 9 presents key demographic and baseline characteristics for the MYR 301 full analysis set. Demographic and baseline characteristics were generally similar among the three study groups.

The median age of all treated patients was [redacted] years (range: [redacted] years). In a retrospective study by Spaan *et al.* (2020), which analysed 107 patients with HBV/HDV coinfection attending an outpatient clinic in London, England, the median age of patients was observed to be 36.0 years (range: 16 to 61 years) (78). In the UK, the implementation of NICE clinical guideline CG165 likely results in an improved HDV diagnosis rate versus that seen in the locations used for data collection in MYR 301, namely Russia, Germany, Italy, and Sweden. As a result, the age of patients enrolled in the MYR 301 study may be slightly higher than what is observed in UK clinical practice.

The majority of patients were white (82.7%), and over half of participants were male (57.3%). Almost half of the subjects ([redacted]) had cirrhosis at the time of enrolment, and [redacted] of subjects had prior treatment with IFN-based therapy (59). UK clinical experts highlighted that most patients with CHD in the UK are offered a treatment course of IFN as per the NICE clinical guideline CG165 (72). These clinical experts were of the belief that the population enrolled in MYR 301 is broadly representative of the patients that they treat in UK clinical practice (31). Notably, in a UK-specific retrospective study conducted by Spaan *et al*. (2020), the median age was 36.0 years (78).

Table 9: Patient demographics and baseline characteristics in MYR 301 (FAS)

Measure	Delayed Treatment (n=51)	BLV 2mg (n=49)	BLV 10mg (n=50)	Total (n=150)
Sex (n, %)				
Male	26 (51.0)	30 (61.2)	30 (60.0)	86 (57.3)
Female	25 (49.0)	19 (38.8)	20 (40.0)	64 (47.2)
Age (Years)				
Mean (SD)	40.5 (7.5)	43.6 (9.0)	41.3 (8.5)	[redacted]
Q1, Q3	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]	[redacted]
Median (IQR)	[redacted]	[redacted]	[redacted]	[redacted]
Race, n (%)				
White	40 (78.4)	41 (83.7)	43 (86.0)	124 (82.7)
Black or African American	0	0	1 (2.0)	1 (0.7)
Asian	11 (21.6)	8 (16.3)	6 (12.0)	25 (16.7)
BMI (kg/m^2), n (%)				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]	[redacted]
Median (IQR)	[redacted]	[redacted]	[redacted]	[redacted]
BMI Categories, n (%)				
<30 kg/m^2	[redacted]	[redacted]	[redacted]	[redacted]
≥30 kg/m^2	[redacted]	[redacted]	[redacted]	[redacted]
Cirrhosis Status, n (%)				
Present	24 (47.1)	23 (46.9)	24 (48.0)	[redacted]
Absent	27 (52.9)	26 (53.1)	26 (52.0)	[redacted]
Child-Pugh Score				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (IQR)	[redacted]	[redacted]	[redacted]	[redacted]
Child-Pugh Class, n (%)				
A	[redacted]	[redacted]	[redacted]	[redacted]
HDV Genotype, n (%)				
HDV Genotype 1	51 (100.0)	49 (100.0)	49 (98.0)	149 (99.3)

HDV Genotype 5	0	0	1 (2.0)	1 (0.7)
HBV Genotype, n (%)				
Genotype A	[redacted]	[redacted]	[redacted]	[redacted]
Genotype D	[redacted]	[redacted]	[redacted]	[redacted]
Genotype E	[redacted]	[redacted]	[redacted]	[redacted]
No data	[redacted]	[redacted]	[redacted]	[redacted]
HBV DNA (log_{10} IU/mL)				
n/nmiss	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	0.885 (0.989)	1.311 (1.300)	1.110 (1.263)	1.098 (1.194)
HDV DNA (log_{10} IU/mL)				
n/nmiss	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
HBeAg Status, n (%)				
Negative	47 (92.2)	45 (91.8)	43 (86.0)	135 (90.0)
HBsAg (log_{10} IU/mL)				
n/nmiss	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	3.676 (0.465)	3.667 (0.511)	3.615 (0.575)	3.653 (0.516)
ALT (U/L)				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Previous IFN- based therapy, n (%)				
No	[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]	[redacted]

Key: ALT: alanine aminotransferase; BLV: bulevirtide; BMI: body mass index; HBeAg: hepatitis B e surface antigen: HBsAg: hepatitis b surface antigen; HBV: hepatitis B virus; HDV: hepatitis delta virus; IFN: interferon; IQR: interquartile range; n/nmiss: number of participants with evaluable/missing data; Q1: first quartile; Q3: third quartile.
Notes: Child-Pugh score and class are presented for cirrhotic patients only, with percentages based on the number of cirrhotic subjects. Assessments of liver fibrosis were performed only for those subjects who consented to undergo a liver biopsy at baseline and Week 48. Percentages were based on the number of subjects within each treatment group.
Source: Tables 9 and 10, MYR 301 CSR (59).

B.2.3.2 MYR 202

B.2.3.2.1 Trial methodology

Table 10: Summary of trial methodology for MYR 202

Trial Number (Acronym)	NCT03546621 (MYR 202)
Location	The study was conducted at 12 sites in Russia and 4 centres in Germany.
Trial design	A multicentre, open-label, randomized Phase 2 clinical study.
Eligibility criteria for participants	Male and female patients with CHD aged 18-65 years with or without liver cirrhosis, and elevated ALT levels (>1 x ULN, but < 10 x ULN) not meeting any exclusion criteria were eligible and included in the study.
Settings and locations where the data were collected	Treatment and all study procedures were performed on an outpatient basis.
Study periods and trial drugs	Eligible patients were randomly assigned to four treatment groups (randomisation ratio 1:1:1:1) stratified by the presence of liver cirrhosis: • **Group A**: BLV 2 mg/day SC for 24 weeks + TDF, with an additional 24-week follow-up period on TDF. • **Group B**: BLV 5 mg/day SC for 24 weeks + TDF, with an additional 24-week follow-up period on TDF. • **Group C**: BLV 10 mg/day SC for 24 weeks + TDF, with an additional 24-week follow-up period on TDF. • **Group D**: treatment with TDF for 48 weeks. The treatment period was 24 weeks, during which 8 visits to the study centre were performed. Five further visits to the study centre occurred during the 24-week follow-up period.
Prior and concomitant Medication	Concomitant medications were allowed in the event of treatment-related AEs in either of the treatment arms.
Primary outcome	HDV RNA response defined as HDV RNA negativation or a decrease by ≥2-$\log_{10}$ IU/mL from baseline to Week 24.
Secondary outcomes used in the model/specified in the scope	• Combined response, defined as HDV RNA response and normal ALT at treatment Week 24 and Week 48. • Changes in ALT values at Weeks 24 and 48 compared to baseline.
Pre-planned subgroups	• Patients with liver cirrhosis • Patient without liver cirrhosis

Key: ALT: alanine aminotransferase; BLV: bulevirtide; CHD: chronic hepatitis delta; CSR: clinical study report; HDV: hepatitis delta virus; RNA: ribonucleic acid; TDF: tenofovir; ULN: upper limit of normal.
Source: MYR 202 CSR (58)

B.2.3.2.2 Trial design

MYR 202 was a randomised, open-label, multicentre Phase 2 clinical study aiming to investigate the efficacy and safety of bulevirtide when administered in combination with TDF compared with TDF alone.

TDF is a highly effective inhibitor of HBV polymerase used to manage the patients underlying HBV infection. HDV usually supresses HBV replication (13), however there is a risk that as HDV is supressed, the suppression of HBV wanes and patients experience a rapid rise in HBV viral load leading to increasing liver damage (12). Therefore, it is important that, where treating patients with CHD, the patient is regularly assessed for concurrent HBV therapy. As a result, TDF was used as a concomitant treatment for subjects randomised into one of the bulevirtide treatment groups and is also used as a monotherapy in the comparator arm of the study.

MYR 202 studied patients with CHD and quantifiable HDV virus replication, including a proportion for whom previous treatment with IFN-based therapy failed or who were considered IFN-based therapy intolerant, as well as patients with compensated cirrhosis.

TDF was administered in all study groups A-D in doses according to the label for HBV infection (97). As described in the decision problem, in the absence of off-label IFN-based therapy, this ongoing treatment of the underlying hepatitis B infection where indicated is considered as BSC.

Eligible patients were randomly assigned to four treatment groups (randomisation ratio 1:1:1:1) stratified by the presence of liver cirrhosis (yes/no):

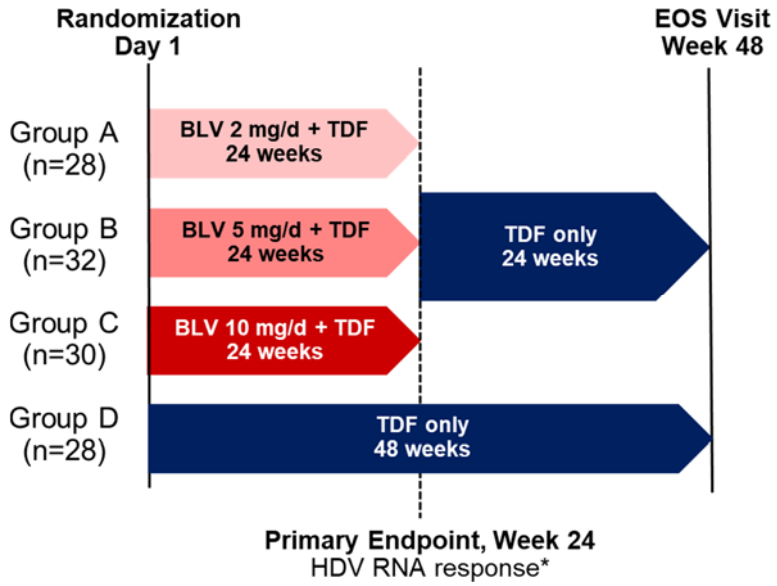
- **Group A**: bulevirtide 2 mg/day SC for 24 weeks + TDF, with an additional 24-week follow-up period on Tenofovir treatment.
- **Group B**: bulevirtide 5 mg/day SC for 24 weeks +TDF, with an additional 24-week follow-up period on tenofovir treatment.
- **Group C**: bulevirtide 10 mg/day SC for 24 weeks, with an additional 24-week follow-up period on TDF treatment.

- **Group D**: TDF for 48 weeks.

Groups A, B and C received different doses of bulevirtide and TDF for 24 weeks, after which there was a follow-up period of 24 weeks with continued TDF treatment only. Patients from group D received TDF during both the treatment period of 24 weeks and during the follow-up period of 24 weeks. Upon the completion of the treatment period, patients entered a 24-week follow up period, resulting in a trial duration of 72 weeks (Figure 8).

During the study, patients in groups A, B and C injected bulevirtide SC once daily (dose dependent on group allocation) and administered TDF orally once daily. Patients allocated to group D received TDF orally once daily (Figure 8).

Figure 8: MYR 202 study design



Key: BLV: bulevirtide; d: day; HDV: hepatitis delta virus; EOS: end of study; RNA: ribonucleic acid; TDF: tenofovir.
Notes: *HDV RNA response defined as a negative PCR result for HDV RNA or a ≥2-$\log_{10}$ IU/mL decline from baseline
Source: MYR 202 CSR (58).

B.2.3.2.3 Eligibility criteria

The key inclusion and exclusion criteria for MYR 202 are described in Table 11.

Table 11: Key eligibility criteria for MYR 202

Key Inclusion Criteria	Key Exclusion Criteria
• Age from 18 to 65 years at the time of ICF signature. • Positive serum HBsAg for at least 6 months before screening. • Positive serum anti-HDV antibody for at least 6 months before screening. • Positive PCR results for serum HDV RNA at screening. • Patients with liver cirrhosis, irrespective of previous IFN treatment*. • Patients without liver cirrhosis, who failed prior IFN treatment or for whom, in the opinion of the investigator, is currently contraindicated (including history of IFN intolerance)**. • ALT level >1 x ULN, but less than 10 x ULN.	• Child-Pugh score of B-C or over 6 points. • Creatine clearance is <60ml/min • HCV or HIV coinfection. Patients with anti-HCV antibodies can be enrolled, if screening HCV RNA test is negative. • Use of IFNs within 30 days before screening. • Malignant tumours in any organ system, including HCC, in the past or current history. • Systemic connective-tissue diseases. • Decompensated liver disease in the current or previous history.

Key: ALT: alanine aminotransferase; HBsAg: hepatitis B surface antigen; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; HDV: hepatitis delta virus; HIV: human immunodeficiency virus; ICF: informed consent form; IFN: interferon; PCR: polymerase chain reaction; RNA: ribonucleic acid; ULN: upper limit of normal.
Notes: *Patients with liver cirrhosis could be included in case the interim analysis provided a positive safety assessment. The sponsor notified the centres on the results of the analysis and the permission to enrol cirrhotic patients. **Patients with previous interferon treatment could be enrolled only at least 20 days after the last interferon dose.
Source: Section 9.3, MYR 202 CSR (58).

For a full list of eligibility criteria please refer to the CSR (58).

B.2.3.2.4 Settings and locations where the data were collected

In MYR 202, a total of 16 centres enrolled at least one subject. These centres were divided across Germany, which contributed four study centres, and Russia, who were responsible for the remaining 12 centres. Treatment and all study procedures were performed on an outpatient basis.

B.2.3.2.5 Trial drugs and concomitant medications

Bulevirtide

In MYR 202, the study drug was bulevirtide. This was provided as a lyophilised powder for single use in sterile vials. The dosages of bulevirtide used in the study were 2, 5 or 10 mg according to the treatment group randomly assigned. Dose adjustment could be performed in groups B and C if a patient developed a study drug-related AE.

TDF

The reference product, TDF (VIREAD®) was provided in the form of a film-coated tablet for oral administration The dosage of TDF used in the study was 254mg (tenofovir disoproxil 245mg, equivalent to tenofovir disoproxil fumarate 300mg).

Concomitant medications

Concomitant medications were allowed in the event of treatment-related AEs in either of the treatment arms.

The following concomitant treatments were prohibited:

- Systemic glucocorticosteroids
- Psychotropic agents, drugs, and psychoactive substances

The use of immunomodulatory agents and antiviral drugs, apart from TDF, had to be discussed with the medical monitor before treatment initiation.

B.2.3.2.6 Outcomes used in the economic model or specified in the scope, including primary outcome

The MYR 202 study assessed the efficacy and safety of bulevirtide (bulevirtide 2 mg, 5 mg, and 10 mg) in suppressing HDV replication in adults with CHD, in combination with TDF over 24 weeks when compared to TDF alone.

The study's primary endpoint was:

- HDV RNA response, defined as HDV RNA negativity or a reduction by ≥2-log_{10} IU/mL from baseline to Week 24.

Key secondary endpoints included:

- Change from baseline in HDV RNA levels
- Changes in ALT values (defined as ALT values ≤ 31 U/L for female patients and ≤ 41 U/L for male patients) at treatment Week 24 and Week 48
- Combined response, defined as the achievement of an HDV RNA response (HDV RNA negativity or ≥2-log_{10} IU/mL decline) and normal ALT simultaneously at Week 24 and Week 48
- Lack of fibrosis progression based on transient elastometry (FibroScan®) at Week 24

Safety was assessed throughout the study by the monitoring of adverse events (AEs), physical examinations, vital signs, 12-lead ECGs, development of anti-bulevirtide antibodies, and clinical laboratory tests (58).

B.2.3.2.7 Patient datasets and baseline characteristics

The baseline characteristics of patients in MYR 202 are shown in Table 12.

Table 12: Patient demographics and characteristics at baseline in MYR 202

	BLV 2 mg + TDF (n=28)	BLV 5 mg + TDF (n=32)	BLV 10 mg + TDF (n=30)	TDF (n=28)	Total: n=118
Sex (n, %)					
Male	15 (53.6)	21 (65.6)	23 (76.7)	20 (71.4)	79 (66.9)
Female	13 (46.4)	11 (34.4)	7 (23.3)	8 (28.6)	39 (33.1)
Age (Years)					
Mean (SD)	39.4 (8.3)	40.9 (9.5)	41.8 (11.3)	38.5 (8.7)	40.2 (9.5)
Q1, Q3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Race (n, %)					
White	21 (75.0)	30 (93.8)	27 (90.0)	23 (82.1)	101 (85.6)
Black or African American	0	1 (3.1)	0	0	1 (0.8)
Asian	7 (25.0)	1 (3.1)	3 (10.0)	5 (17.9)	16 (13.6)
BMI (kg/m^2), n (%)					
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI Categories					
<30 kg/m^2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥30 kg/m2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cirrhosis Status, n (%)					
Present	15 (53.6)	15 (46.9)	16 (53.3)	13 (46.4)	59 (50.0)
Absent	13 (46.4)	17 (53.1)	14 (46.7)	15 (53.6)	59 (50.0)
HDV RNA (log_{10} IU/mL)					
n/miss	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ALT (U/L)					
Mean (SD)	97.1 (65.2)	123.1 (80.2)	122.7 (84.1)	118.6 (87.6)	115.8 (79.5)
Previous IFN-based therapy (>30 days prior to screening), n (%)					
No	8 (28.6)	17 (53.1)	16 (53.3)	10 (35.7)	51 (43.2)
Yes	20 (71.4)	15 (46.9)	14 (46.7)	18 (64.3)	67 (56.8)

Key: ALT: alanine aminotransferase; BLV: bulevirtide; HDV: BMI: body mass index; hepatitis delta virus, IFN: interferon; RNA: ribonucleic acid.
Notes: Percentages are based on the number of participants within each treatment group.
Source: Tables 13, MYR 202 CSR (58).

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 MYR 301

B.2.4.1.1 Analysis population

All analyses of the efficacy endpoints were performed using the FAS and the PPAS. If the randomised analysis set differed from the size of the FAS by more than 10%, the analysis of the primary efficacy variable was also to be performed on the randomised analysis set (59).

The analysis of safety was performed on the safety analysis set (SAS), defined as all participants randomised to delayed bulevirtide treatment or randomised to bulevirtide and who received bulevirtide at least once after randomisation (59).

B.2.4.1.2 Sample size

To account for the repeated analysis of response, the nominal 2-sided significance level of 0.05 was split among the 2 time points, with 0.01 for Week 24 leaving 0.04 for Week 48. At each time point, the bulevirtide doses were compared with delayed treatment in terms of a hierarchical testing procedure, starting with the higher dose at the respective adjusted 2-sided significance levels (59).

The expected response rates at Week 48 for the bulevirtide 2 mg and 10 mg doses were at least 45%. The conservative expectation for the delayed treatment response rates was 8% or less. These assumptions were based on results from the preceding Phase 2 MYR 202 study (59).

With a sample size of 47 participants per treatment group, a Fisher's exact test with a 0.04 2-sided significance level had 97.8% power to detect this between the individual bulevirtide treatment groups and the delayed treatment group proportions. The power to reject both null hypotheses simultaneously was 95.6% (59).

The sample size was increased slightly to 50 subjects per treatment group to account for few potential early withdrawals before exposure. Hence, 150 participants were planned to be randomised (59).

B.2.4.1.3 Statistical analysis

A summary of statistical analyses for MYR 301 is available in Table 13.

Table 13: Summary of statistical analyses: MYR 301

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
NCT03852719 (MYR 301)	The null hypothesis tested in this study was that there was no clinically significant difference in the proportion of responders to BLV compared to the delayed treatment group.	Two-sided Fisher's exact tests were used to compare the response rates in each of the BLV treatment groups compared to the delayed treatment group. All CIs were presented as two-sided with a nominal confidence of 95% for within groups, unless otherwise stated.	A sample size of 50 subjects was to provide approximately 97.8% power to detect a difference in response between the separate BLV treatment groups and the delayed treatment response group, using a Fisher's exact test with a 2-sided 0.04 significance level.	LOCF was used to impute missing values for the combined response if the missing value was related to COVID-19; otherwise, the MEF approach was employed. Subjects with a missing assessment at 48 weeks for HDV RNA or ALT were considered non-responders.

Key: ALT: alanine aminotransferase; BLV: bulevirtide; CI: confidence interval; HDV: hepatitis delta virus; LOCF: last observation carried forward; MEF: missing equals failure; RNA: ribonucleic acid.
Source: MYR 301 CSR (59).

Primary efficacy analysis

For the primary analysis, two-sided Fisher's exact tests at an overall significance level of 0.05 were performed to compare the response rates for each treatment group. In terms of a hierarchical testing procedure, the second null hypothesis was not rejected if the first null hypothesis could not be rejected (59).

The primary efficacy endpoint was summarised using counts and percentages, together with a 95% exact (Clopper-Pearson) confidence interval (CI) for the true percentage (59).

Due to the expected low number of responders under delayed treatment, the analysis was not stratified by cirrhosis (yes/no) or other covariables (59).

Secondary efficacy analysis

For the key secondary endpoint, defined as undetectable HDV RNA at Week 48, the same 2-step approach as described for the primary endpoint was used. Two-sided Fisher's exact tests were performed for each of the bulevirtide treatment groups compared with the control group of the delayed treatment. A hierarchical testing procedure was also used for this endpoint, where a two-sided Fisher test was only performed if both primary null hypotheses were rejected. To maintain control of the family-wise error rate, the same nominal levels of significance used for the primary analyses were also used (59).

The proportions of participants with ALT normalisation at Week 48 for each of the bulevirtide treatment groups were compared with the control group of delayed treatment using Fisher's exact test. Exact unconditional CIs based on scores for the proportion differences were calculated, with corresponding CIs of 95% (59).

As the first and only baseline measurement for liver stiffness (as measured by elastography) occurred at Week 48, the main analysis of this endpoint was analysed using analysis of covariance without repeated measures (59).

Subgroup analyses

All descriptive summaries of efficacy data were presented for the subgroups based on the presence of cirrhosis for both the FAS and PPAS (59).

Safety analyses

All evaluations of safety data were performed on the SAS (59).

B.2.4.1.4 Participant flow

Details of participant flow in MYR 301 are provided in Appendix D1.2.

B.2.4.2 MYR 202

B.2.4.2.1 Analysis population

The primary endpoint was analysed in the modified intention-to-Treat (mITT) set, defined as all randomised patients who received at least one dose of the study treatment. The data was also analysed in the Per Protocol (PP) population, which defined as a subset of mITT population completed the 24-week treatment period who had no major protocol violations (58).

Safety evaluation parameters were analysed in the safety analysis set, which was defined as all subjects who received at least one dose of the study medication in the bulevirtide groups or tenofovir in group of observation after randomisation (58).

B.2.4.2.2 Sample size

Using a two-sided test with a power of 80%, a significance level of $\alpha\alpha$ = 0.05⁄3 ≈ 0.0167 (using Bonferroni correction to adjust for multiple testing; the three active treatment groups were tested separately against the control group), and a superiority limit (test margin) of 5%, a sample size of 28 patients per group was deemed sufficient to detect a 34% increase in response compared to the control group, assuming a response rate of 3% for the control group.

Assuming a drop-out rate of 5%, a total number of 30 patients per treatment group where needed (58).

B.2.4.2.3 Statistical analysis

A summary of the statistical analyses for MYR 202 is available in Table 14.

Table 14: Summary of statistical analyses: MYR 202

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
NCT03546621 (MYR 202)	The null hypothesis tested in this study was that there was no clinically significant difference in the proportion of responders to BLV compared to the tenofovir group.	Unless otherwise stated, two-sided significance tests were used to compare the proportion of responders in each BLV treatment group compared to the TDF only group. Two-sided 95% CIs were calculated using the Clopper-Pearson method.	Using a two-sided test with a power of 80%, a significance level of $\alpha\alpha$ = 0.05⁄3 ≈ 0.0167 (using Bonferroni correction to adjust for multiple testing; the three active treatment groups were tested separately against the control group), and a superiority limit (test margin) of 5%, a sample size of 28 patients per group was deemed sufficient to detect a 34% increase in response compared to the control group, assuming a response rate of 3% for the control group. Assuming a drop-out rate of 5%, a total	No imputations of missing data were performed, and the analyses were performed on the observed cases, unless otherwise stated. For all response parameters, the MEF approach were used for the main analysis on the mITT analysis set (i.e., patients with missing data were considered as non-responders).

			number of 30 patients per treatment group where needed.	

Key: BLV: bulevirtide; CI: confidence interval; MEF: missing equals failure; mITT: modified intention-to-treat; TDF: tenofovir.
Source: MYR 202 CSR (58).

Primary efficacy endpoint

Per protocol, the primary efficacy analysis was carried out when all bulevirtide - treated patients had completed the 24-week treatment period. One-sided continuity-corrected Wald tests for superiority, with the superiority limit set to 5%, were used to test null hypotheses of no clinically significant difference in the proportion of responders compared to the TDF only group at Week 24. Separate comparisons were made for each of the three bulevirtide treatment groups, and adjusted p-values were computed using the Bonferroni-Holm method (58).

As supportive analysis, Fisher's exact test was used to test a null hypothesis of no difference in proportions of responders in a two-sided alternative hypothesis. Separate tests were performed for each of the three bulevirtide treatment groups against the TDF only group at Week 24 (58).

The primary efficacy endpoint was summarised using counts and percentages, together with a 95% exact (Clopper-Pearson) CI for the true percentage (58).

Secondary efficacy endpoints

For the analysis of secondary efficacy endpoints, van Elteren tests and Fisher's exact tests were used to compare differences between bulevirtide in combination of TDF and TDF alone (58).

Safety analyses.

All evaluations of safety data were performed on the SAS (58).

B.2.4.2.4 Participant Flow

Details of participant flow in MYR 202 are provided in Appendix D1.2.

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

The critical appraisal of MYR 301 and MYR 202 was conducted using the quality assessment tool developed by the University of York's Centre for Reviews and Dissemination (CRD), as recommended by NICE (98). Full results are presented in appendix D1.3.

B.2.6 Clinical effectiveness results of the relevant studies

Summary of clinical effectiveness results

- The efficacy and safety of bulevirtide in the treatment of adults with CHD has been demonstrated in a pivotal multicentre, open-label, randomised MYR 301 trial.
- The MYR 301 population presented a group with particularly poor prognosis, with [redacted] of patients cirrhotic at baseline, and [redacted] having failed prior therapy with IFN.
- [redacted] of the bulevirtide 2 mg treated participants achieved the primary efficacy endpoint of combined response at Week 48, compared with [redacted] of participants in the delayed treatment group ([redacted]).
- A subgroup analysis demonstrates that subjects naïve to treatment with IFN demonstrate a combined response consistent with those with prior IFN exposure, supporting consistency of response.
- The proportions of participants achieving HDV RNA response at Week 48 in the bulevirtide 2 mg treatment group was [redacted], compared with [redacted] in the delayed treatment group ([redacted]).
- The bulevirtide 2 mg treatment group achieved ALT normalisation in [redacted] of participants, compared with [redacted] of delayed treatment group participants ([redacted]).

- The efficacy and safety of bulevirtide in the treatment of adults with CHD was also investigated in a smaller multicentre, open-label, randomized MYR 202 trial, where HDV RNA response at Week 24 was observed in 53.6% of participants treated with bulevirtide 2 mg + TDF, compared to 3.6% of participants receiving TDF alone (p<0.0001).

B.2.6.1 MYR 301

Bulevirtide is indicated for adults with CHD who have compensated liver disease, and evidence of significant fibrosis (METAVIR stage greater than or equal to F2), whose disease has responded inadequately to IFN-based therapy, or who are ineligible to receive IFN-based therapy due to intolerance or contraindication.

As discussed in Section B.2.7, subgroup analyses based on prior IFN-based therapy suggests that the achievement of a combined response is consistent amongst IFN-based therapy naïve patients and those with prior IFN-based therapy exposure (99). IFN-based therapy has a different mechanism of action, and thus there is no clinically plausible reason why a patient treated with IFN-based therapy could not demonstrate a meaningful response after treatment with bulevirtide.

In addition, as outlined in Section B.2.12, due to the orphan nature of the disease (26), only 150 patients were recruited for the MYR 301 study, who were randomised in a 1:1:1 ratio to one of three treatment groups (~50 patient per arm). In view of the relatively small sample size, and consistency shown between subgroups, we present results of the full MYR 301 population in this submission. For further detail on how response differs by subgroup, please see Section B.2.7.

B.2.6.1.1 Results of primary outcome

The primary outcome of MYR 301 was a combined response at Week 48, as defined in Section B.2.3.1.6. As the bulevirtide marketing authorisation is for 2 mg bulevirtide dose, the data for the 10 mg arm are not summarised herein.

At Week 48, there was a statistically significant treatment effect for subjects receiving bulevirtide 2 mg compared with subjects in the delayed treatment group

([redacted]). The proportion of patients who achieved a combined response was [redacted] ([redacted] subjects, 95% CI: [redacted]) in the bulevirtide 2 mg group, compared to [redacted] ([redacted] subjects, 95% CI: [redacted]) in the delayed treatment arm (59).

At Week 24, the proportion of patients who achieved a combined response in the bulevirtide 2 mg treatment arm was 36.7% (18 of 49 subjects, 95% CI: [redacted]) (59). The observed increase in the proportion of responders from Week 24 to Week 48 is consistent with the mechanism of action of bulevirtide, which prevents the infection of new hepatocytes but does not inhibit virus production by cells infected prior to treatment initiation (see Section B.1.2). Thus, it is possible that, as infected hepatocytes continue to be cleared by the immune system alongside bulevirtide preventing the infection of new cells, the proportion of responders may increase further with continued treatment beyond Week 48. It is anticipated that longer-term data at Week 96 will become available in [redacted] which will provide further evidence of the benefit of continued treatment with bulevirtide.

In addition, post-hoc analyses visualising the evolution of ALT improvement for patients showing a virologic response show [redacted] (see Figure 29, Appendix N). [redacted] (see Figure 30, Appendix N), [redacted] (see Figure 31, Appendix N) (100).

Furthermore, as the inclusion criteria for ALT level ranged between >1x ULN to 10x ULN, many patients may have experienced a significant benefit with bulevirtide but will not be classified as a responder to treatment. As demonstrated in Figure 29 and Figure 30 in Appendix N, [redacted]

[redacted] (100).

In this regard, the continued improvement in ALT levels over time demonstrates an evolving level of response. Data collection is still ongoing with MYR 301, with 96-week data expected to become available in [redacted].

Figure 9: Combined response at Weeks 24 and 48 (FAS; MYR 301)

Key: BLV: bulevirtide; CI: confidence interval; FAS: full analysis set.
Notes: Mean data with error bars representing 95% CI are shown. Combined response was defined as undetectable HDV RNA (HDV RNA <LLoD, where LLoD=6 IU/mL) or decrease in HDV RNA by ≥2-$\log_{10}$ IU/mL from baseline, and ALT normalisation (defined as an ALT value within the normal range).
Source: Table 14.2.1-1, MYR 301 CSR (59).

Similar results were obtained in the analysis of the combined response in the PPAS at Weeks 24 and 48, as a supportive analysis to the main FAS analysis. At Weeks 24 and 48, in the bulevirtide 2 mg group, [redacted] ([redacted] subjects, 95% CI: [redacted]) and [redacted] ([redacted] subjects, 95% CI: [redacted]) of participants, respectively, were responders, compared to no responders and [redacted] ([redacted] subjects, 95% CI: [redacted]) of participants in the delayed treatment group. A statistically significant difference ([redacted]) in the proportion of responders was observed between the bulevirtide 2 mg group and the delayed treatment group at both timepoints (59).

B.2.6.1.2 Results of secondary and exploratory outcomes

HDV RNA decrease by ≥2-log_{10} IU/mL or undetectable HDV RNA at Week 48

A statistically significant difference was observed between the 2 mg bulevirtide treatment group and the delayed treatment arm ([redacted]). Overall, [redacted] of subjects ([redacted] subjects, 95% CI: [redacted]) in the bulevirtide 2 mg group achieved a virologic response at Week 48. Only [redacted] of participants ([redacted] subjects, 95% CI: [redacted]) in the delayed treatment arm demonstrated a virologic response (59).

The consensus from the 2019 EASL-AASLD Conference was that a 2-log_{10} decrease in HDV RNA might suffice as a primary endpoint for clinical trials for a maintenance treatment for CHD (25). In MYR 301, viral response was defined as either of the following virologic parameters:

- HDV RNA decrease by ≥2-log_{10} IU/mL from baseline
- Undetectable HDV RNA

ALT normalisation at Week 48

Statistically significant differences in ALT normalisation were observed in the 2 mg bulevirtide treatment group at both Week 48 and Week 24 ([redacted]) compared to the delayed treatment arm (59). ALT normalisation was achieved at Week 48 by [redacted] of participants ([redacted] subjects, 95% CI: [redacted]) in the bulevirtide 2 mg treatment group. Only [redacted] of participants ([redacted] subjects, 95% CI: [redacted]) in the delayed treatment arm achieved ALT normalisation (Table 15) (59).

The proportion of participants demonstrating a response remained relatively constant across both treatment groups from Week 24 to Week 48. At Week 24, the proportion of participants demonstrating ALT normalisation was 53.1% (26 of 49 subjects, 95% CI: [redacted]) in the bulevirtide 2 mg treatment group, while only 5.9% (3 of 51 subjects, 95% CI: [redacted]) of participants in the delayed treatment arm achieved ALT normalisation (59).

Table 15: ALT normalisation at Weeks 24 and 48 (FAS; MYR 301)

	Delayed Treatment (n=51)	BLV 2mg (n=49)
Week 24		
Number of subjects included in analysis	51	49
Number of responders	3	26
Proportion with ALT normalisation, % (95% CI)	5.9 ( )	53.1 ( )
Difference in proportions, % (99% CI)	—	47.2 ( )
p value	—	
Week 48		
Number of subjects included in analysis		
Number of responders		
Proportion with ALT normalisation, % (95% CI)		
Difference in proportions, % (99% CI)	—	
p value	—	

Key: ALT: alanine aminotransferase; BLV: bulevirtide; CI: confidence interval; FAS: full analysis set.
Notes: A confidence level of 95% is used for within group CIs and for CIs in different proportions. Fisher's exact tests were used for each comparison of BLV 2 mg and 10 mg versus delayed treatment using a significance level of 0.05.
Source: Table 14.2.2.2-1, MYR 301 CSR (59).

HDV RNA decrease by ≥2-$\log_{10}$ IU/mL at Week 48

At Week 48, the proportion of responders observed to have an HDV RNA decrease by ≥2-$\log_{10}$ IU/mL (>99%) from baseline increased to (subjects, 95% CI:) in the bulevirtide 2 mg group. No additional responders were observed in the delayed treatment arm (59).

An HDV RNA decrease by ≥2-$\log_{10}$ IU/mL from baseline at Week 24 was observed in 55.1% (27 of 49 subjects, 95% CI:) of participants in the bulevirtide 2 mg treatment group. Only 3.9% (2 of 51 subjects, 95% CI:) of participants in the delayed treatment arm achieved a ≥2-$\log_{10}$ IU/mL from baseline (Table 16) (59).

Table 16: HDV RNA decrease by ≥2-$\log_{10}$ IU/mL at Weeks 24 and 48 (FAS; MYR 301)

	Delayed Treatment (n=51)	BLV 2mg (n=49)
Week 24		
Number of subjects included in analysis	51	49
Number of responders	2	27
Proportion of responders, % (95% CI)	3.9 ( )	55.1 ( )
Difference in proportions, % (99% CI)	—	
p value	—	
Week 48		
Number of subjects included in analysis		
Number of responders		
Proportion of responders, % (95% CI)		
Difference in proportions, % (99% CI)	—	
p value	—	

Key: BLV: bulevirtide; CI: confidence interval; FAS: full analysis set; HDV: hepatitis delta virus; RNA: ribonucleic acid.
Notes: A confidence level of 95% is used for within group CIs. For difference in proportions, the confidence level used is 99% for 24 weeks and 96% for week 48. Fisher's exact tests were used for each comparison of BLV 10 mg versus BLV 2 mg and using a significance level of 0.05.
Source: Table 14.2.3.3-1, MYR 301 CSR (59).

Undetectable HDV RNA at Week 48

There was a positive trend for the proportion of subjects experiencing undetectable HDV RNA from baseline to Week 48. The proportion of responders in the bulevirtide 2 mg group from Week 24 to Week 48. The proportion of responders with undetectable HDV RNA at Week 48 was (subjects, 95% CI:). There was no statistical difference between the proportion of responders with undetectable HDV RNA levels between the bulevirtide 2 mg group and the delayed treatment group (59).

At Week 24, the proportion of responders with undetectable HDV RNA was 6.1% (3 of 49 subjects, 95% CI:) in the bulevirtide 2 mg treatment group. There was no statistically significant difference observed in HDV RNA undetectability between the active treatment group and the delayed treatment arm.

There were with undetectable HDV RNA in the delayed treatment group at any time point, including Week 48 (Table 17) (59). As highlighted in Section

B.1.3.3, BSC, defined as ongoing treatment for underlying hepatitis B infection, does not have a meaningful effect on HDV RNA levels in patients with CHD (27).

Table 17: Undetectable HDV RNA at Weeks 24 and 48 (FAS; MYR 301)

	Delayed Treatment (n=51)	BLV 2mg (n=49)
Week 24		
Number of subjects included in analysis	51	49
Number of responders	0	3
Proportion of responders, % (95% CI)	0.0 (—)	6.1 ([redacted])
Difference in proportions (99% CI)	—	[redacted]
p value	—	[redacted]
Week 48		
Number of subjects included in analysis	[redacted]	[redacted]
Number of responders	[redacted]	[redacted]
Proportion of responders, % (95% CI)	[redacted] (—)	[redacted]
Difference in proportions (99% CI)	—	[redacted]
p value	—	[redacted]

Key: BLV: bulevirtide; CI: confidence interval; FAS: full analysis set.
Notes: A confidence level of 95% is used for within group CIs. For difference in proportions, the confidence level used is 99% for 24 weeks and 96% for week 48. Fisher's exact tests were used for each comparison of BLV 10 mg versus BLV 2 mg and using a significance level of 0.01 at Week 24.
Source: Table 14.2.2.1-1, MYR 301 CSR (59).

Change from baseline in liver stiffness and histological activity at Week 48

FibroScan® assessment of liver stiffness acts as an early marker for evaluating the severity and prognosis of CHD, as the amount of liver fibrosis is correlated with the future risk of developing cirrhosis and liver-related complications (101).

At Week 48, the FibroScan® measurement of liver stiffness indicated that the bulevirtide 2 mg ([redacted] kPa) group had a decrease in liver stiffness from baseline. Conversely, subjects in the delayed treatment group ([redacted] kPa) experienced a significant increase in liver stiffness over 48 weeks ([redacted]) (Table 18). A decrease in liver stiffness (measured by FibroScan®) confirms an improvement in the clinical status of the participants treated with the licensed 2 mg dosage of bulevirtide. It can represent a decline in liver inflammation, as well as an improvement in liver fibrosis (59).

Table 18: Liver stiffness (FibroScan®) at Week 48 (FAS; MYR 301)

	Delayed Treatment (n=51)	BLV 2mg (n=49)
Baseline		
n/miss	[redacted]	[redacted]
Mean, kPa (SD)	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Median (IQR)	[redacted]	[redacted]
Week 48		
n/miss	[redacted]	[redacted]
Mean, kPa (SD)	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Median (IQR)	[redacted]	[redacted]
Change from baseline to Week 48		
n/miss	[redacted]	[redacted]
Mean, kPa (SD)	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Median (IQR)	[redacted]	[redacted]

Key: BLV: bulevirtide; FAS: full analysis set; IQR: interquartile range; kPa: kilopascal; n/miss: number of subjects with evaluable/missing data; SD: standard deviation; Q1: first quartile; Q3: third quartile.
Notes: Baseline is defined as the last valid evaluation prior to the first dose of study medication for bulevirtide 2 mg and last value before or at randomisation for the delayed treatment.
Source: Table 14.2.2.3-3, MYR 301 CSR (59).

Aside from the liver stiffness measurements summarised above, assessments of liver fibrosis were performed only for those subjects who consented to undergo a liver biopsy at baseline and Week 48. For [redacted] of 51 subjects ([redacted]) in the delayed treatment group and [redacted] of 49 participants ([redacted]) in the bulevirtide 2 mg group, biopsy data were unavailable for these assessments and considered 'missing' (101).

In the subset of participants with available data, the percentage of subjects who experienced an improvement in METAVIR fibrosis stage was numerically higher in the bulevirtide 2 mg treatment group compared to the delayed treatment arm (Table 19) (101).

Table 19: Change in METAVIR fibrosis stage to Week 48 (FAS; MYR 301)

METAVIR fibrosis stage	Delayed Treatment (n=26)	BLV 2mg (n=25)
Improvement %, (95% CI)	[redacted]	[redacted]
No change %, (95% CI)	[redacted]	[redacted]
Worsening %, (95% CI)	[redacted]	[redacted]

Key: BLV: bulevirtide; FAS: full analysis set.
Notes: Percentages are based on the number of subjects within each treatment group with observed data. Percentage for 'missing. Category is based on the number of subjects within each treatment group. Improvement is defined as a decrease of at least one point; worsening is defined as an increase of at least one point.
Source: Table 14.2.3.1-1, MYR 301 CSR (59).

In addition, an exploratory sub-study of MYR 301 by Allweiss *et al*. (2021) took core liver biopsies from a subgroup of patients treated with bulevirtide at baseline and Week 48. The frequency of HDV antigen (HDAg) positive hepatocytes declined by median [redacted] in the bulevirtide 2 mg treatment group, with [redacted] subjects ([redacted]) achieving an undetectable HDAg. A median increase in HDAg-positive hepatocytes of [redacted] was observed in the delayed treatment group, with only [redacted] subjects ([redacted]) experiencing undetectable HDAg (80).

The amount of HDAg-positive hepatocytes strongly correlated with intrahepatic HDV RNA levels. At Week 48, a median [redacted] decline in intrahepatic HDV RNA levels was observed in the bulevirtide 2 mg group, with [redacted] subjects ([redacted]) achieving undetectable HDV RNA. Such a strong reduction in intrahepatic HDV RNA levels further supports the novel mechanism of action of bulevirtide. In the delayed treatment group, a median intrahepatic HDV RNA increase of [redacted] was observed, with [redacted] participants ([redacted]) achieving undetectable HDV RNA (80). Changes in host gene expression also correlated with HDV viral load. This indicates that the therapeutic reduction of HDV viral load also diminishes liver inflammation (80).

There is the possibility that responding to treatment may induce a regression in liver fibrosis and cirrhosis for those achieving a combined response, as has been observed upon NA treatment of HBV monoinfected patients (102). In a previous study in patients with hepatitis delta responding to PEG-IFN therapy, Farci *et al*. (2004) reported regression in four of six patients with sustained biochemical

response. These patients had active cirrhosis in their first three liver biopsies and an absence of fibrosis in their last liver biopsy. The publication concluded that there was an association between fibrosis regression and a significant decrease in HDV viral load (103).

EQ-5D-3L at Week 48

A summary of the EQ-5D-3L data for the bulevirtide 2 mg group and the delayed treatment arm can be found in Table 20 and Table 21.

Table 20: EQ-5D-3L evaluation summary by level and visit in the bulevirtide 2 mg group (FAS; MYR 301)

Dimension	Category, n (%)	Baseline (n=49)	Week 24 (n=49)	Week 48 (n=49)
Mobility	No problems			
	Some problems			
	Extreme problems			
	Missing			
Self-care	No problems			
	Some problems			
	Extreme problems			
	Missing			
Performance of usual activities	No problems			
	Some problems			
	Extreme problems			
	Missing			
Pain/discomfort	No problems			
	Some problems			
	Extreme problems			
	Missing			
Anxiety/depression	No problems			
	Some problems			
	Extreme problems			
	Missing			

Key: BLV: bulevirtide; FAS: full analysis set.
Notes: Baseline is defined as the last valid evaluation prior to the first dose of study medication for bulevirtide 2 mg and 10 mg, and last value before or at randomisation for the delayed treatment. Percentages are based on the number of subjects within each treatment group. For the FAS, subjects are analysed as randomised (i.e., planned treatment).
Source: Tables 14.2.3.9-11, 14.2.3.9-17, 14.2.3.9-23, 14.2.3.9-29, and 14.2.3.9-35, MYR 301 CSR (59).

Table 21: EQ-5D-3L evaluation summary by level and visit in the delayed treatment group (FAS; MYR 301)

Dimension	Category, n (%)	Baseline (n=51)	Week 24 (n=51)	Week 48 (n=51)
Mobility	No problems	[redacted]	[redacted]	[redacted]
	Some problems	[redacted]	[redacted]	[redacted]
	Extreme problems	[redacted]	[redacted]	[redacted]
	Missing	[redacted]	[redacted]	[redacted]
Self-care	No problems	[redacted]	[redacted]	[redacted]
	Some problems	[redacted]	[redacted]	[redacted]
	Extreme problems	[redacted]	[redacted]	[redacted]
	Missing	[redacted]	[redacted]	[redacted]
Performance of usual activities	No problems	[redacted]	[redacted]	[redacted]
	Some problems	[redacted]	[redacted]	[redacted]
	Extreme problems	[redacted]	[redacted]	[redacted]
	Missing	[redacted]	[redacted]	[redacted]
Pain/discomfort	No problems	[redacted]	[redacted]	[redacted]
	Some problems	[redacted]	[redacted]	[redacted]
	Extreme problems	[redacted]	[redacted]	[redacted]
	Missing	[redacted]	[redacted]	[redacted]
Anxiety/depression	No problems	[redacted]	[redacted]	[redacted]
	Some problems	[redacted]	[redacted]	[redacted]
	Extreme problems	[redacted]	[redacted]	[redacted]
	Missing	[redacted]	[redacted]	[redacted]

Key: BLV: bulevirtide; FAS: full analysis set.
Notes: Baseline is defined as the last valid evaluation prior to the first dose of study medication for bulevirtide 2 mg and 10 mg, and last value before or at randomisation for the delayed treatment. Percentages are based on the number of subjects within each treatment group. For the FAS, subjects are analysed as randomised (i.e., planned treatment).
Source: Tables 14.2.3.9-11, 14.2.3.9-17, 14.2.3.9-23, 14.2.3.9-29, and 14.2.3.9-35, MYR 301 CSR (59).

At Week 48, scores for the individual EQ-5D-3L domains, EuroQol Visual Analogue, fatigue severity scale, and Hepatitis Quality of Life Questionnaire™ (HQLQ) components were [redacted] between the bulevirtide 2 mg treatment group compared with the delayed treatment group (59).

For the QoL analysis, although inferential statistics (p values) were presented, the results should be interpreted with caution as multiple endpoints were tested, and the study was not powered to test these exploratory endpoints (59).

Overall, a large proportion of evaluable subjects in the bulevirtide 2 mg group experienced no problems with mobility ([redacted]), self-care ([redacted]), or with the performance of usual activities ([redacted]) at baseline. With regards to pain/discomfort, [redacted] subjects ([redacted]) in the bulevirtide 2 mg group reported some problems at baseline, which after treatment declined to [redacted] subjects ([redacted]) at Week 48. In contrast, within the delayed treatment group, the proportion of patients reporting some problems with pain/discomfort did not show a large decline from baseline to Week 48, changing from [redacted] ([redacted] subjects) to [redacted] ([redacted] subjects) of participants (59).

Similarly, [redacted] subjects ([redacted]) reported experiencing anxiety/depression at baseline in the bulevirtide 2 mg treatment arm, with [redacted] reporting an extreme problem. By Week 48, only [redacted] subjects ([redacted]) in the bulevirtide 2 mg treatment arm experienced problems with anxiety/depression, with [redacted] patients reporting extreme problems (59). However, the same magnitude of effect was not observed in the delayed treatment arm. A total of [redacted] subjects ([redacted]) in the delayed treatment arm reported some problems at baseline, which after treatment declined to [redacted] subjects ([redacted]) at Week 48. The proportion of patients experiencing extreme problems with anxiety/depression remained unchanged from baseline to Week 48 ([redacted]) (59).

Statistical analysis using the observed odds ratios (OR) for each of the five dimensions of EQ-5D-3L [redacted] between the delayed treatment group and the bulevirtide 2 mg treatment group at Week 48 (59).

The total mean VAS score was [redacted] (range: [redacted]) at screening and increased over time, with higher mean score of [redacted] (range: [redacted]) at Week 24, and [redacted] (range: [redacted]) at Week 48. At Week 48, the largest increase in mean VAS score was found in the bulevirtide 2 mg group (mean score of [redacted], range: [redacted]), while the delayed treatment group had a mean increase from baseline of [redacted] (range: [redacted]) (Figure 10) (59).

Figure 10: Mean VAS score (FAS; MYR 301)

[redacted]

Key: BLV: bulevirtide; FAS: full analysis set; VAS: visual analogue scale.
Notes: Scale represents point score value (0-100), where 0=worst health state and 100=best health state) on the visual analogue scale.
Source: Table 14.2.3.9-43, MYR 301 CSR (59).

Given the general scarcity of quantitative data on health utilities for patients with HDV, it is important to assess the utility values reported in the MYR 301 clinical trial to evaluate their validity. The EQ-5D-3L data collected at baseline in this study indicated that disease EQ-5D-3L scores did not differ by cirrhosis status; patients with no cirrhosis at baseline had an EQ-5D-3L score of [redacted], compared to [redacted] for patients with cirrhosis at baseline (59). Clinical experts confirmed that a difference of just [redacted] was an unexpected result (31). As highlighted in Section B.1.3.2, people with HDV and cirrhosis have a greater risk for liver-related events than those without cirrhosis (see Figure 3) (38).

Furthermore, these findings are inconsistent with previous research that indicates cirrhosis negatively affects patients' HRQoL. A study in HBV infected patients in Canada reported EQ-5D-3L utility values of 0.920 and 0.880 in patients without and with compensated liver cirrhosis respectively (104), while a study in China also reported a higher EQ-5D-3L utility value for patients without liver cirrhosis (0.800) versus patients with compensated liver cirrhosis (0.700) (105). Similarly, a meta-analysis of patients with HCV infection reported EQ-5D-3L values of 0.829 and 0.717 for patients with and without compensated liver cirrhosis, respectively (106).

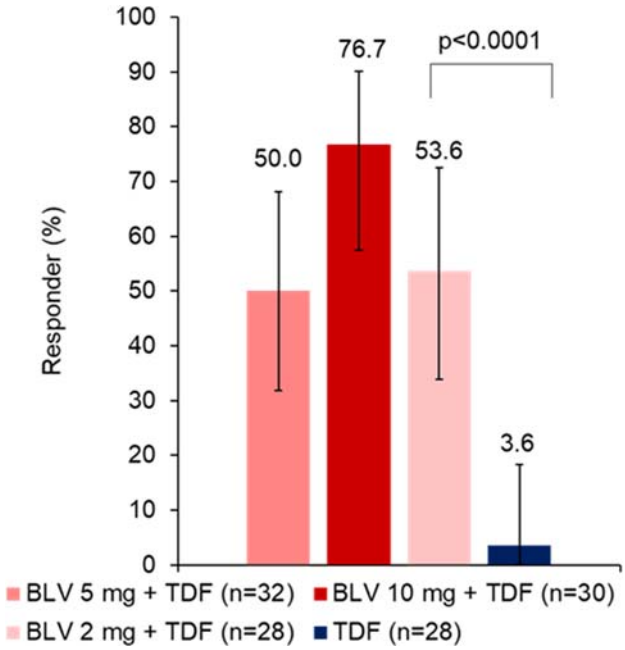
B.2.6.2 MYR 202

MYR 202 was a dose ranging Phase 2 study which assessed the efficacy and safety of bulevirtide (2, 5, or 10 mg) in supressing HDV replication in adults with CHD, in combination with TDF over 24 weeks compared to TDF alone. Efficacy data for the bulevirtide 2 mg treatment and TDF monotherapy treatment arms are summarised herein. Note however, that solely the 2 mg dose has marketing authorisation.

B.2.6.2.1 Results of primary outcome

A significant HDV RNA response was observed in 53.6% (15 of 28 subjects, 95% CI: 33.9%, 72.5%) of participants treated in the bulevirtide 2 mg + TDF treatment group ($p<0.0001$). No substantial HDV RNA response was observed in the TDF treatment arm, with only 3.6% (1 of 28 subjects, 95% CI: 0.1%, 18.3%) of participants achieving the primary endpoint (Figure 11) (58).

Figure 11: HDV RNA response at Week 24 (mITT)



Key: BLV: bulevirtide; CI: confidence interval; HDV: hepatitis delta virus; mITT: modified intention-to-treat; RNA: ribonucleic acid; TDF: tenofovir.
Notes: Error bars representing 95% CI are shown. HDV RNA response was defined as a negative PCR result of HDV RNA (undetectable HDV RNA or a ≥2-$\log_{10}$ IU/mL decline from baseline to Week 24.
Source: Table 16, MYR 202 CSR (58).

B.2.6.2.2 Results of relevant secondary outcomes

Change from Baseline in HDV RNA Levels at Week 24 and Week 48

A significant mean decline in HDV RNA levels from baseline of -1.918 $\log_{10}$ IU/mL was observed in the bulevirtide 2 mg + TDF treatment group (p<0.0001), while no significant decline in HDV RNA level was seen in the TDF monotherapy group (58).

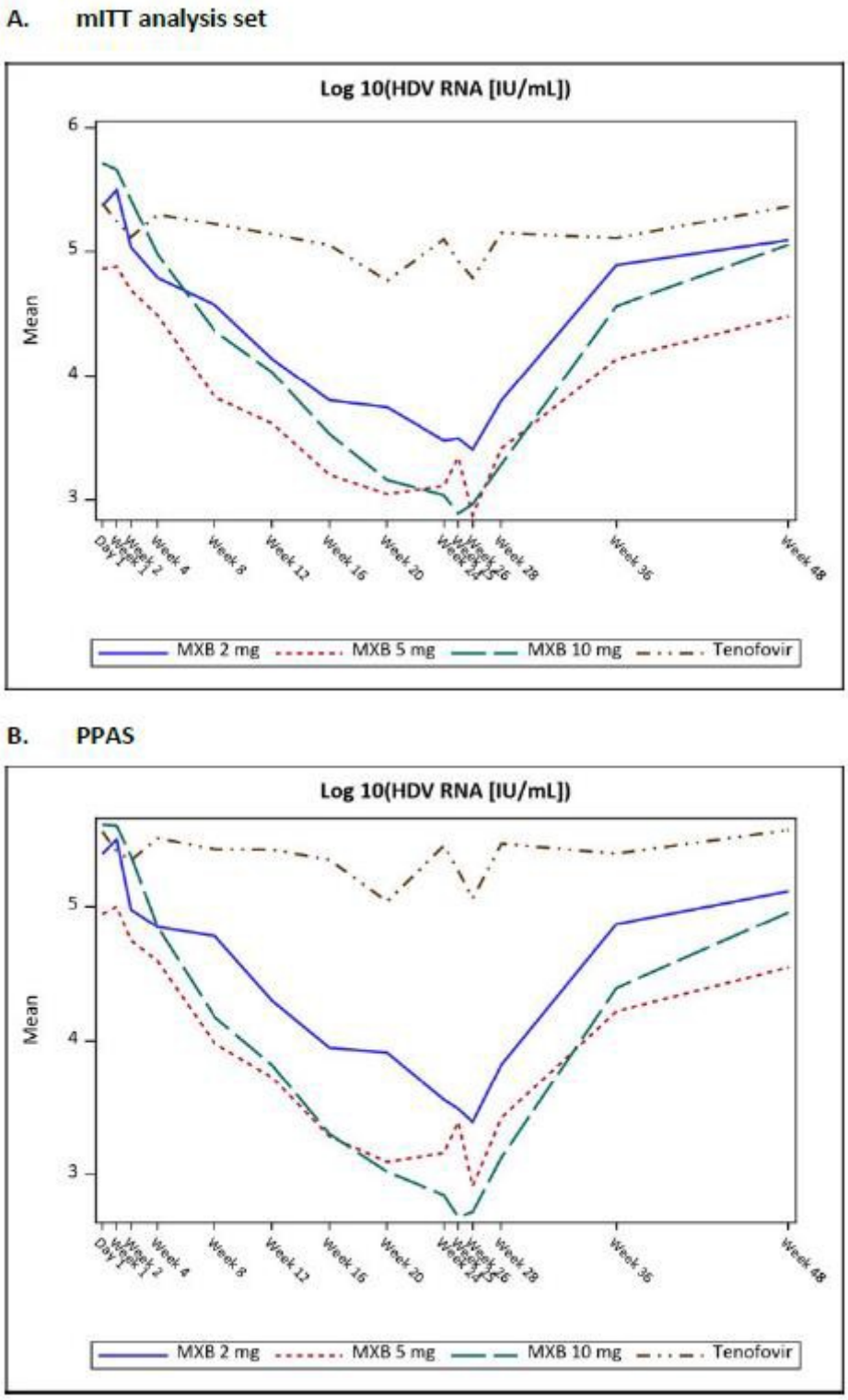
After treatment cessation with bulevirtide, mean HDV RNA rebounded to baseline values by Week 48 (Figure 12; Table 22). As demonstrated in Section B.2.6.1, the continuation of bulevirtide treatment beyond 24 weeks is associated with an increasing number of virologic responders. Given the increase in responder rate, the optimal treatment duration of bulevirtide monotherapy may exceed 48 weeks (58), with the current bulevirtide licence stating that 'treatment should be continued as long as associated with clinical benefit.'

Table 22: Summary statistics on log-10 transformed HDV RNA levels (mITT)

Mean Log_{10} HDV RNA, IU/mL] (SD)	TDF (n=28)	BLV 2 mg + TDF (n=28)	BLV 5 mg + TDF (n=32)	BLV 10 mg + TDF (n=30)
Baseline				
Mean (SD)	5.393 (1.351)	5.345 (1.157)	4.874 (1.398)	5.688 (0.983)
Week 24				
Mean (SD)	5.099 (1.394)	3.478 (1.613)	3.114 (1.659)	3.040 (1.118)
Mean CfB (SD)	-0.175 (0.806)	-1.918 (1.186)	-1.758 (1.149)	-2.594 (0.652)
Week 48				
Mean (SD)	5.368 (1.568)	5.092 (1.426)	4.483 (1.823)	5.055 (1.358)
Mean CfB (SD)	0.085 (0.608)	-0.239 (0.951)	-0.408 (1.289)	-0.611 (1.073)

Key: BLV: bulevirtide; CfB: change from baseline; HDV: hepatitis delta virus; RNA: ribonucleic acid.
Notes: Baseline is defined as the last valid evaluation prior to the first dose of study medication.
Source: Table 19, MYR 202 CSR (58).

Figure 12: Mean log_{10} transformed HDV RNA levels over time



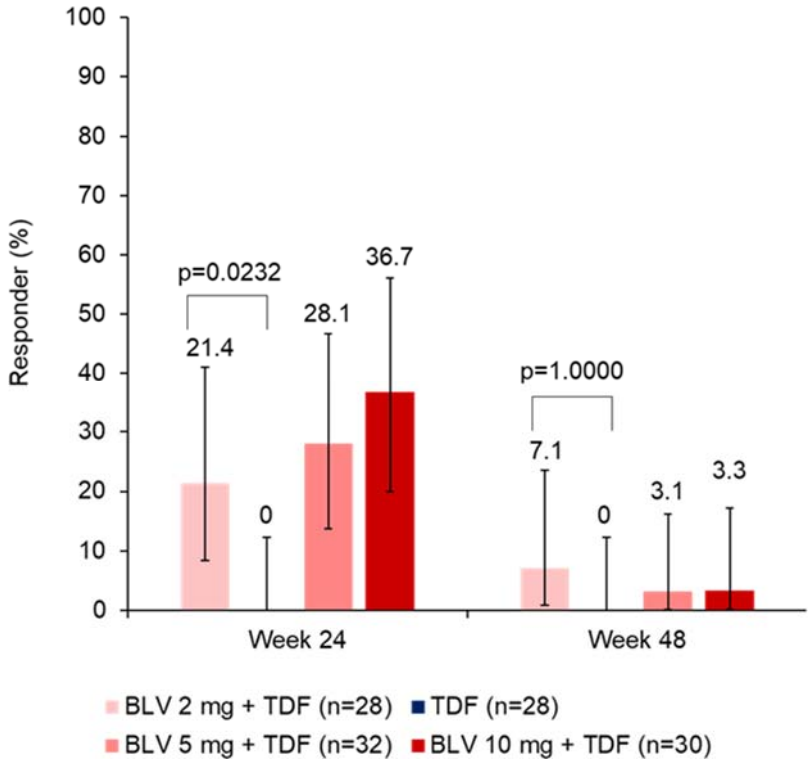
Key: HDV: hepatitis delta virus; mITT: modified intention-to-treat; MXB, myrcludex B (now known as bulevirtide); PPAS: per protocol analysis set; RNA: ribonucleic acid.
Notes: (A) Changes in mean log_{10} transformed HDV RNA levels from baseline to Week 48 in the mITT analysis set. (B) Changes in mean log_{10} transformed HDV RNA levels from baseline to Week 48 in the PPAS.
Source: Figures 14.2.2.1 and 14.2.2.2 (58).

Combined response at Week 24 and Week 48

At Week 24, the proportion of patients with a combined response was significantly higher in the bulevirtide 2 mg + TDF treatment group versus the TDF monotherapy arm. At the end of treatment, 21.4% (6 of 28 subjects, 95% CI: 8.3%, 41.0%) of participants in the bulevirtide 2 mg + TDF treatment group achieved a combined response. No case of combined response was observed in the TDF monotherapy group at Week 24 (Figure 13) (58).

Furthermore, 28.1% (9 of 32 subjects, 95% CI: 13.7%, 46.7%) of participants achieved a combined response in the bulevirtide 5 mg + TDF treatment arm, while 36.7% (11 of 30 subjects, 95% CI: 19.9%, 56.1%) of participants demonstrated a combined response in the bulevirtide 10 mg + TDF treatment cohort (Figure 13) (58).

Figure 13: Combined response at Weeks 24 and 48 (mITT)



Key: BLV: bulevirtide; CI: confidence interval; HDV: hepatitis delta virus; mITT: modified intention-to-treat; RNA: ribonucleic acid; TDF: tenofovir.
Notes: Percentages are based on the number of participants within each treatment group. Error bars representing 95% CI are shown. Combined response was defined as an HDV RNA response (undetectable HDV RNA or a ≥2-$\log_{10}$ IU/mL decline from baseline) and ALT normalisation.
Source: Table 25, MYR 202 CSR (58).

Change in ALT values at Week 24 and Week 48

After 24 weeks of treatment, a significantly higher proportion of patients treated with bulevirtide 2 mg + TDF had normal ALT levels compared to patients receiving TDF monotherapy ($p<0.005$). Normal ALT levels were achieved by 42.9% (12 of 28 subjects, 95% CI: 24.5%, 62.8%) of participants, while only 7.1% (2 of 28 subjects, 95% CI: 0.9%, 23.5%) of subjects in the TDF monotherapy group demonstrated achieved normal ALT levels (58).

By Week 48, at 24 weeks post-treatment discontinuation, there was no significant difference in the proportion of patients with normal ALT levels between the bulevirtide 2 mg + TDF treatment group and the TDF monotherapy arm ($p>0.05$). In the bulevirtide 2 mg + TDF treatment group, the proportion of subjects with normal ALT levels had reduced to 14.3% (4 of 28 subjects, 95% CI: 4.0%, 32.7%). On the other hand, the TDF monotherapy group demonstrated a small increase in ALT response, with 14.3% (4 of 28 subjects, 95% CI: 4.0%, 32.7%) of participants achieving ALT normalisation (58).

An equally high level of response at Week 24 was observed across the bulevirtide 5 mg + TDF and bulevirtide 10 mg + TDF treatment groups, with normalised ALT achieved in 50.0% (16 of 32 subjects, 95% CI: 31.9%, 68.1%) and 40.0% (95% CI: 22.7%, 59.4%) of subjects respectively. At Week 48, 24 weeks post-treatment discontinuation, no significant difference in the proportion of patients with normal ALT values between the treatment groups was demonstrated ($p<0.005$). The level of response in the bulevirtide 5 mg + TDF and bulevirtide 10 mg + TDF also reduced to 3.1% (1 of 32 subjects, 95% CI: 0.1%, 16.2%) and 10.0% (3 of 30 subjects, 95% CI: 2.1%, 26.5%) respectively (58).

Lack of fibrosis progression based on transient elastometry (FibroScan®) at Week 24

At Week 24, larger mean decreases in liver stiffness were observed in all bulevirtide groups compared to the TDF only group. The mean change from baseline at Week

24 for BLV 2 mg + TDF was -2.85 ± 2.65 kPa compared to -0.78 ± 3.17 kPa for TDF only (58).

Table 23: Mean change in liver stiffness (FibroScan®) from baseline (mITT; MYR 202)

	TDF (n=28)	BLV 2 mg + TDF (n=28)	BLV 5 mg + TDF (n=32)	BLV 10 mg + TDF (n=30)
Baseline				
Mean, kPa (SD)	16.20 (7.83)	14.45 (6.37)	17.18 (11.49)	16.00 (7.37)
95% CI	(12.30, 20.10)	(11.38, 17.52)	(12.44, 21.92)	(12.30, 20.10)
Week 24				
Mean, kPa (SD)	12.35 (6.14)	11.31 (5.29)	14.12 (9.96)	12.00 (6.19)
95% CI	(9.19, 15.51)	(8.96, 13.66)	(10.09, 18.14)	(9.26, 14.75)
Change from baseline to Week 24				
Mean, kPa (SD)	-0.78 (3.17)	-2.85 (2.65)	-2.52 (6.21)	-3.38 (3.83)
95% CI	(-2.61, 1.05)	(-4.13, -1.58)	(-5.21, 0.17)	(-5.17, -1.59)

Key: BLV: bulevirtide; CI: confidence interval; kPa: kilopascals; mITT: modified intention-to-treat; SD: standard deviation; TDF: tenofovir.
Source: Table 14.2.9.1, MYR 202 CSR (58).

B.2.6.3 Summary of results

The efficacy and safety of bulevirtide for the treatment of adults with CHD was investigated in the multicentre, open-label, randomised pivotal Phase 3 MYR 301 trial, as well as the supporting MYR 202 clinical study.

The MYR 301 population represented a group with particularly poor prognosis, with [redacted] of patients cirrhotic at baseline, and [redacted] having failed prior therapy with IFN-based therapy (59). Clinical experts suggested that the baseline characteristics observed were generalisable to patients currently seen in UK clinical practice (31). However, in a 2020 retrospective study, Spaan *et al*. found a lower median age of 36.0 years in a UK population (78).

Overall, [redacted] of patients in the bulevirtide 2 mg treatment group achieved a combined response at Week 48, compared to just [redacted] in the delayed treatment arm ([redacted]) (59). Data from previous studies suggests that patients achieving undetectable HDV RNA or a ≥2-$\log_{10}$ decline in HDV RNA levels, and ALT

normalisation, are at a reduced risk of developing complications of liver disease, such as HCC, cirrhosis, decompensation, and death (20,35,36,61).

The combined response composite endpoint sets a high bar for level of response, given it requires the fulfilment of two surrogate outcomes. When analysing the individual components of the combined response, [redacted] of patients in the bulevirtide 2 mg treatment group achieved undetectable HDV RNA or a ≥2-log_{10} decline in HDV RNA levels at Week 48, compared to just [redacted] in the delayed treatment arm ([redacted]). With regards to ALT normalisation, [redacted] of subjects achieved normal ALT levels at Week 48, compared to [redacted] in the delayed treatment arm ([redacted]) (59). In patients who demonstrated a >2-log_{10} reduction in HDV RNA, but failed to achieve the combined endpoint, [redacted] (see Appendix N; Figure 29). [redacted] (see Appendix N; Figure 30), [redacted] (107). By also taking into account the innovative mechanism of action of bulevirtide, the proportion of responders is predicted to increase further beyond Week 48. In this regard, data collection is still ongoing with MYR 301, with 96-week data expected to become available in [redacted].

Furthermore, at Week 48, the FibroScan® measurement of liver stiffness indicated that the bulevirtide 2 mg ([redacted] kPa) group had a significant decrease in liver stiffness from baseline compared to the delayed treatment group ([redacted] kPa) (59). In addition, an exploratory substudy of MYR 301 found that there was a strong correlation between HDV RNA and HDAg levels, which demonstrates that the number of infected hepatocytes reduced (80). As established by Farci *et al*. (2004), there is an association between fibrosis regression and a significant decrease in HDV viral load (103), which would suggest that patients responding to bulevirtide could experience an improvement in fibrosis and cirrhosis.

The multicentre, open-label, randomised supporting Phase 2 MYR 202 study further supports the efficacy and safety of bulevirtide, albeit over a shorter 24-week

treatment period. Similar to MYR 301, the MYR 202 population represented a group with a poor prognosis, with 50.0% of patients cirrhotic at baseline, and 56.8% having failed prior IFN-based therapy (58).

The MYR 202 study assessed the efficacy and safety of bulevirtide in suppressing HDV replication in adults with CHD, in combination with TDF, over a shorter 24-week treatment period. The trial achieved its primary endpoint of an HDV RNA response at Week 24, which was observed in 53.6% of participants treated with bulevirtide 2 mg + TDF, compared to 3.6% of participants receiving TDF alone. Furthermore, treatment with bulevirtide 2 mg + TDF was associated with a statistically significantly higher proportion of participants achieving a combined response at Week 24 compared to TDF monotherapy (58).

In summary, bulevirtide has demonstrated unprecedented efficacy in a population of adults with CHD with compensated liver disease. Evidence from the MYR 301 and MYR 202 clinical studies demonstrates that treatment with bulevirtide results in a greater proportion of individuals achieving a combined response, HDV RNA decline or suppression, and ALT normalisation, compared to BSC or delayed treatment. The proposed population highlighted in the decision problem currently has no existing treatment options. Thus, as the only approved treatment for CHD, bulevirtide represents an important therapeutic option to address the rapid progression of the disease in this population and reduce the risk of developing severe liver-related complications including cirrhosis, HCC, decompensation and death.

B.2.7 Subgroup analysis

A pre-planned subgroup analysis of virologic and biochemical response was defined to greater characterise patient populations for whom bulevirtide could provide the greatest benefit. These endpoints were analysed in the same manner as the primary efficacy endpoint. The subgroups analysed were:

- People with cirrhosis (METAVIR fibrosis stage F4).
- People without cirrhosis (METAVIR fibrosis stage F0-F3).

The proportion of patients demonstrating a combined response was consistent amongst patients with and without cirrhosis (59). At Week 48, [redacted] of 23 subjects ([redacted]) with cirrhosis showed a combined response, compared with [redacted] of 24 subjects ([redacted]) in the delayed treatment arm ([redacted]). Similarly, [redacted] of 26 subjects ([redacted]) without cirrhosis also demonstrated a combined response, while [redacted] of the 27 subjects without cirrhosis in the delayed treatment arm showed a combined response to treatment ([redacted]) (See Table 82; Appendix E) (59).

Given the proposed positioning of bulevirtide, a post-hoc subgroup analysis was undertaken to greater characterize whether prior treatment with IFN-based therapy impacts response to bulevirtide. This subgroup was defined based on data from prior medication for which the preferred name includes the word 'interferon'. The list of medications satisfying this condition are as follows:

- Peginterferon alfa-2a
- Peginterferon alfa-2b
- Interferon alfa-2b
- Interferon alpha
- Peginterferon
- Interferon
- Cepeginterferon alfa-2b
- Interferon alfa-2a
- Interferon beta-1b

Subgroup analyses suggests that the achievement of a combined response is consistent amongst IFN-based therapy naïve patients and those with prior IFN-based therapy exposure (99). At Week 48, [redacted] subjects ([redacted]) naïve to IFN-based therapy demonstrated a combined response, in comparison to [redacted]

subjects ([redacted]) who had experienced prior IFN treatment. In the delayed treatment arm, only [redacted] patients ([redacted]) who experienced prior IFN-based therapy demonstrated a combined response, in comparison to no subjects in the IFN-based therapy-naïve subgroup (Table 83; Appendix E) (59). As highlighted in Section B.2.6.1, there was not expected to be any difference in the proportion of responders between the two subgroups, given that IFN-based therapy has a different mechanism of action to bulevirtide.

Results of the subgroup analyses are presented in Appendix E.

B.2.8 Meta-analysis

The objective of the meta-analysis was to conduct a relative efficacy and safety comparison of bulevirtide 2 mg monotherapy versus BSC or relevant comparators for CHD treatment (108).

A total of 19 studies from 63 publications were included in the SLR. Across these 19 studies, two studies evaluated bulevirtide 2mg as monotherapy, and one study each evaluated bulevirtide 2 mg in combination with TDF or PEG-IFN. For methods and results of the SLR, please refer to Appendix D1.1.

A comparison of bulevirtide 2 mg, either as a monotherapy or in combination with TDF, is available from the pivotal Phase 3 MYR 301 and Phase 2 MYR 202 clinical studies. MYR 301 compared bulevirtide 2 mg versus delayed treatment, while MYR 202 compared bulevirtide in combination with TDF against TDF alone. As highlighted in Section B.2.3.2, TDF is classified as an NA, and is recommended to manage the patients underlying HBV infection (13). NAs are commonly used medications in hepatitis D, as highlighted in the MYR 301 study, whereby 60.0% of patients received concomitant antiviral treatment (69). The efficacy of TDF monotherapy and delayed treatment is assumed to be similar. Hence, these are marked under one treatment group, termed NA therapy (NAT; referred to previously as NA throughout the submission), in the forthcoming figures to form a comparator for meta-analysis (108).

The DMA was performed using the Sidak–Jonkman [random effect] and Mantel-Haenszel methods [fixed effect] using Stata 17 (Version 17.0, StataCorp, College Station, Texas 77845 USA) (108).

Although we present the results of the DMA compared to NAs, this does not inform the economic model. Instead, data from the pivotal MYR 301 study was used in the economic analyses to inform the relative efficacy and safety of bulevirtide versus BSC. The economic model includes an extrapolation of clinical response data beyond the trial observation period, therefore use of the MYR 301 data ensured consistency of outcomes between different timepoints and between bulevirtide and BSC. Furthermore, whilst figures were generated based on the original NMA report and thus include reference to PEG-IFN, the text focuses on the comparison with BSC as this is relevant for the submission (108).

Further detail on the methodology and results of the DMA can be found in the accompanying NMA report (108).

B.2.8.1 Feasibility assessment

A feasibility assessment study for indirect comparisons of bulevirtide versus BSC was conducted. Table 24 presents the list of studies included in for the DMA base-case analyses (108).

Table 24: List of studies included in the DMA base-case

Comparison	Study name	Treatment 1	Treatment 2
BLV 2 mg monotherapy or combination with TDF versus TDF or delayed treatment	MYR 202	BLV 2 mg/day SC + TDF 245 mg/day po	TDF 245 mg/day po
	MYR 301	BLV 2 mg/day SC	Delayed treatment

Key: BLV: bulevirtide; mg: milligram; NA: nucleos(t)ide analogue; µg: microgram; PO: per oral; SC: subcutaneous; TDF: tenofovir; WK: weekly.
Source: Adapted from Table 7, NMA report (108).

Table 25 highlights the differences across certain baseline characteristics collected in each of the studies confirmed in the DMA base-case analyses. Low heterogeneity was observed across the patient characteristics for MYR 202 and MYR 301 (108).

Table 25: Patient characteristics of studies considered for DMA base-case

Study name	Males (%)	Age (years) Mean/Median	ALT at baseline (IU/L) Mean/Median	Previous IFN treatment (%)	HDV RNA negative (%)	Cirrhosis (%)
MYR 202	67.5	40.2	115.8	56.8	0.8	50.0
MYR 301	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: ALT: alanine aminotransferase; HDV: hepatitis delta virus; IFN: interferon; RNA: ribonucleic acid.
Source: Appendix B – feasibility assessment slides, NMA report (108).

B.2.8.2 Outcomes selected and assessed for analysis

The report of key outcomes at Week 48 in the included studies is summarised below in Table 26.

Table 26: Summary of outcomes reported across included studies at Week 48

Outcome	MYR 202	MYR 301
HDV RNA undetectable	-	✓
HDV RNA undetectable or reduced	✓*T	✓*
Combined response [HDV RNA undetectable or reduced (≥2-log_{10}) and ALT normalisation]	✓T	✓
ALT normalisation	✓T	✓
HDV RNA change from baseline	✓T	✓
ALT change from baseline	✓T	✓
Any AEs	✓T	✓
Any SAEs	✓T	✓
Any Grade 3 or higher AEs	✓T	✓
Treatment discontinuation due to AEs	✓T	✓a

ncluded in base-case analysis; Not included in base-case analysis but included in the sensitivity analysis; Not included in analysis.

Key: AE: adverse event; ALT: Alanine aminotransferase; HDV: hepatitis delta virus; mg: milligram; RNA: ribonucleic acid; SAE: serious adverse event
Notes: *≥2-log_{10} HDV RNA decline or undetectable; TTDF treatment in all arms for 24 weeks.
Source: Adapted from Table 10, NMA report (108).

B.2.8.3 Results

B.2.8.3.1 Combined response at Week 48

A statistically higher proportion of patients treated with bulevirtide 2 mg experienced a combined response compared to NA monotherapy [OR: [redacted] using Sidik-Jonkman model; OR: [redacted] using Mantel-Haenszel model] (Figure 14) (108).

Figure 14: Summary plot of meta-analysis for combined response at Week 48

Key: BLV: bulevirtide; CI: confidence interval; DT: delayed treatment; mg: milligram; OR: odds ratio; TDF: tenofovir.
Notes: In MYR 202, patients received bulevirtide for 24 weeks only, after which all treatment arms received TDF for 24 weeks.
Source: Adapted from NMA report (108).

B.2.8.3.2 Undetectable HDV RNA or reduction (≥2-log10) at Week 48

At Week 48, bulevirtide showed statistically better results compared to NAs [OR: [redacted] using Sidik-Jonkman model; OR: [redacted] using Mantel-Haenszel model] (Figure 15) (108).

Figure 15: Summary plot of meta-analysis for undetectable HDV RNA or reduction (≥2-log$_{10}$) at Week 48

Key: BLV: bulevirtide; CI: confidence interval; DT: delayed treatment; HDV: hepatitis delta virus; mg: milligram; OR: odds ratio; RNA: ribonucleic acid; TDF: tenofovir.
Notes: In MYR 202, patients received bulevirtide for 24 weeks only, after which all treatment arms received TDF for 24 weeks.
Source: Adapted from NMA report (108).

B.2.8.3.3 ALT normalisation at Week 48

At Week 48, a statistically significantly greater proportion of patients treated with bulevirtide 2 mg experienced ALT normalisation compared to NA treatment [OR: [redacted] using Mantel-Haenszel model]. While the direction of the results for the Sidik-Jonkman model was aligned to the results of the Mantel-Haenszel model, statistical significance was not reached [OR: [redacted] using Sidik-Jonkman model] (Figure 16) (108).

Figure 16: Summary plot of meta-analysis for ALT normalisation at Week 48

Key: ALT: alanine aminotransferase; BLV: bulevirtide; CI: confidence interval; DT: delayed treatment; mg: milligram; OR: odds ratio; TDF: tenofovir.
Notes: In MYR 202, patients received bulevirtide for 24 weeks only, after which all treatment arms received TDF for 24 weeks.
Source: Adapted from NMA report (108).

B.2.8.4 Conclusions

Overall bulevirtide 2mg monotherapy has statistically significantly better efficacy than NA monotherapy in terms of the combined response (ALT normalisation and HDV RNA loss or ≥2-$\log_{10}$ reduction), HDV RNA response, and ALT normalisation at Week 48.

B.2.9 Indirect and mixed treatment comparisons

Not applicable.

B.2.10 Adverse reactions

B.2.10.1 MYR 301

The safety and tolerability of bulevirtide for the treatment of adult CHD was evaluated as a secondary outcome in MYR 301. The SAS included all patients randomised to the delayed treatment group, or randomised to bulevirtide and received bulevirtide at least once after randomisation. AEs were coded with the Medical Dictionary for Regulatory Activities (MedDRA) version 24.0 (59).

A total of 150 subjects were enrolled for the Phase 3 MYR 301 study, of which 99 participants received at least one dose of bulevirtide. The remaining 51 participants randomised to the delayed treatment group did not receive bulevirtide before the data cut--off date for the Week 48 primary endpoint analysis. Few doses of the study drug were missed across both treatment groups (Table 27). The mean (SD) rate of compliance for bulevirtide up to Week 48 was similar for both active treatment arms: [redacted] ([redacted]) in the bulevirtide 2 mg group and [redacted] ([redacted]) in the bulevirtide 10 mg treatment group. There were some recorded protocol deviations related to treatment compliance, which have been previously described in Section B.2.4.1. The mean (SD) duration of treatment across the bulevirtide 2 mg and bulevirtide 10 mg treatment groups was [redacted] ([redacted]) weeks and [redacted] ([redacted]) weeks, respectively (59).

Table 27: Missed doses of bulevirtide at Week 48 (SAS; MYR 301)

	Delayed Treatment (n=51)	BLV 2mg (n=49)
Number of missed bulevirtide doses		
Mean (SD)	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Median (IQR)	[redacted]	[redacted]
Proportion missed bulevirtide doses (%)		
Mean (SD)	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Median (IQR)	[redacted]	[redacted]

Key: BLV: bulevirtide; IQR: interquartile range; Q1: first quartile; Q3: third quartile; SAS: safety analysis set; SD: standard deviation.
Notes: For the SAS, participants were analysed as treated (i.e., actual treatment). For one participant, number and proportion of missed doses are set to missing as discovery date was several months after expected Week 24 date.
Source: Table 29, MYR 301 CSR (59).

B.2.10.1.1 Summary of adverse events

In total, [redacted] treatment emergent adverse events (TEAEs) were reported in [redacted] subjects ([redacted]) during the first 48 weeks of the MYR 301 study, with [redacted] TEAEs reported in [redacted] participants ([redacted]) in the bulevirtide 2 mg treatment group, less than [redacted] the number seen in the bulevirtide 10mg group ([redacted] TEAEs in [redacted] subjects). TEAEs related to bulevirtide were recorded in [redacted] subjects ([redacted]) in the bulevirtide 2 mg treatment group, compared to [redacted] subjects ([redacted]) in the bulevirtide 10 mg treatment arm. Adverse events were graded by the investigator according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 5 (109). Overall, the majority of TEAEs were Grade 1 (mild) or Grade 2 (moderate) in severity. A similar percentage of participants in each treatment group experienced any TEAEs Grade 3 or higher. No deaths occurred and there were no TEAEs reported which led to withdrawal from the study (59).

Table 28: Overview of AEs (SAS; MYR 301)

	Delayed Treatment (n=51)	BLV 2mg (n=49)	BLV 10mg (n=50)	Total (n=150)
Total number of AEs, n	[redacted]	[redacted]	[redacted]	[redacted]
Any AE, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAE, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Any serious TEAE, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAE leading to the withdrawal of the study medication, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAE leading to death, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
TEAE by severity, n (%)				
Grade 1 (mild)	[redacted]	[redacted]	[redacted]	[redacted]
Grade 2 (moderate)	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3 (severe)	[redacted]	[redacted]	[redacted]	[redacted]
Grade 4 (life-threatening or disabling)	[redacted]	[redacted]	[redacted]	[redacted]
Grade 5 (death)	[redacted]	[redacted]	[redacted]	[redacted]
TEAE by causality, n (%)				
Reasonable possibility	[redacted]	[redacted]	[redacted]	[redacted]
No reasonable possibility	[redacted]	[redacted]	[redacted]	[redacted]
Not applicable	[redacted]	[redacted]	[redacted]	[redacted]

Key: AE: adverse event; BLV: bulevirtide; TDF: TEAE: treatment emergent adverse event; SAS: safety analysis set.
Notes: AEs were coded according to MedDRA Version 24.0. TEAEs began on or after the drug start up date up to 30 days after permanent discontinuation of the study drug, or led to premature study drug discontinuation. For the delayed treatment group, TEAEs began on or after the randomisation date up to the Week 48 visit date, or up to study discontinuation date if discontinued study before the Week 48 visit.
Source: Table 30, MYR 301 CSR (59).

B.2.10.1.2 Common adverse events

TEAEs that occurred in ≥5% of participants across any treatment group in the SAS are summarised in Table 29 (59).

Table 29: AEs in ≥5% of patients in any treatment group (SAS; MYR 301)

AE by Preferred Term	Delayed Treatment (n=51)	BLV 2mg (n=49)	BLV 10mg (n=50)
Subjects with any TEAE, n (%)	[redacted]	[redacted]	[redacted]
Vitamin D deficiency	[redacted]	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]
Eosinophilia	[redacted]	[redacted]	[redacted]
ALT increased	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]
Abdominal pain upper	[redacted]	[redacted]	[redacted]
Injection site reaction	[redacted]	[redacted]	[redacted]
Proteinuria	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]
Injection site erythema	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]
Injection site pruritus	[redacted]	[redacted]	[redacted]
AST increased	[redacted]	[redacted]	[redacted]
Injection site swelling	[redacted]	[redacted]	[redacted]
Sleep disorder	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]
Bradycardia	[redacted]	[redacted]	[redacted]

Key: AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BLV: bulevirtide; SAS: safety analysis set; TEAE: treatment emergent adverse event.
Notes: Percentages are based on the number of participants treated with BLV.
Source: Table 31, MYR 301 CSR (59).

The most common Grade 3 TEAEs, experienced in >1 patient across the treatment groups, were [redacted] and [redacted]. [redacted] was observed in [redacted] subjects ([redacted] subjects in the delayed treatment arm, [redacted] subjects ([redacted]) in the bulevirtide 2 mg treatment group, and [redacted] subjects ([redacted]) in the bulevirtide 10 mg treatment arm. [redacted] was observed in the delayed treatment arm and bulevirtide 10 mg treatment group in [redacted] subjects ([redacted] and [redacted] participants ([redacted]) respectively. No Grade 4 TEAEs were recorded across the study groups (59).

B.2.10.1.3 Summary of serious adverse events

A similar percentage of participants experienced a serious adverse event (SAE) across each treatment group (Table 30). SAEs were observed in [redacted] ([redacted]) in the bulevirtide 10 mg and delayed treatment arms, and in [redacted] ([redacted]) within the bulevirtide 2 mg treatment arm. None of the SAEs were considered related to the study drug by investigators (59).

There were no SAEs reported for >1 participant in any of the treatment groups. [redacted] participants experienced more than one SAE: [redacted] in the delayed treatment group experienced [redacted] and [redacted], and [redacted] in the bulevirtide 2 mg treatment group experienced [redacted] and [redacted] (59).

Table 30: SAEs reported across any treatment group (SAS; MYR 301)

SAE by Preferred Term	Delayed Treatment (n=51)	BLV 2mg (n=49)	BLV 10mg (n=50)
Subjects with any SAE, n (%)	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]
Cholelithiasis	[redacted]	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]	[redacted]
COVID-19 pneumonia	[redacted]	[redacted]	[redacted]
Depression	[redacted]	[redacted]	[redacted]
Foot fracture	[redacted]	[redacted]	[redacted]

Key: BLV: bulevirtide; SAE: serious adverse event; SAS: safety analysis set.
Notes: Percentages are based on the number of participants within each treatment group.
Source: Table 33, MYR 301 CSR (59).

B.2.10.1.4 Adverse events of special interest

The preferred terms for the AEs of interest were defined by selecting relevant preferred terms based on MedDRA Version 24.0 (59).

Increased bile salts

Bile salt elevations are mechanistically due to the binding of the NTCP receptor by bulevirtide. Per the study protocol, if an increase of total bile salts above ULN was both asymptomatic and judged by the investigator to be clinically insignificant, it was not reported as an AE, which was the case for the vast majority of bile salt increases over 48 weeks. Bile salts have been reported in the literature to be associated with skin conditions. Due to the effect of bulevirtide on increasing levels of bile salts, particular attention was paid to skin disorders, and the anaphylactic/anaphylactoid response. No participants experienced an anaphylactic reaction or anaphylactoid response. Whilst the bile salt levels in the bulevirtide 10 mg group were higher than the bulevirtide 2 mg group as expected, there was no clear correlation between the presence of pruritus and the levels of bile salts in either the bulevirtide 2 mg or bulevirtide 10 mg dose (59).

Hepatic Safety

In the MYR 301 SAS, potential hepatic flare AEs were experienced by a similar percentage of participants in the delayed treatment group ([redacted]), the bulevirtide 2 mg treatment group ([redacted]), and the bulevirtide 10 mg treatment group ([redacted]). All potential hepatic flare AEs were Grade 1 or Grade 2 in severity, and none resulted in discontinuation of the study drug (59).

The AEs meeting the definition of potential hepatic flare by treatment group were as follows:

- **Delayed treatment group**: ALT and aspartate aminotransferase (AST) increased ([redacted]); and gamma-glutamyl transferase (GGT) increased ([redacted]).

- **Bulevirtide 2 mg treatment group**: ALT increased, hyperbilirubinemia, and blood bilirubin increased ([redacted]); and AST increased and hepatic pain ([redacted]).
- **Bulevirtide 10 mg treatment group**: ALT increased ([redacted]); hyperbilirubinemia and GGT increased ([redacted]); and AST increased, blood bilirubin increased, and hepatic pain ([redacted]) (59).

[redacted] participants ([redacted]) in the bulevirtide 2 mg treatment group and [redacted] participants ([redacted]) in the bulevirtide 10 mg treatment group had potential hepatic flares considered related to bulevirtide. Of these [redacted] subjects, [redacted] had the potential hepatic flare AE resolved and [redacted] subject in the bulevirtide 10 mg group had an unresolved hepatic flare (59).

[redacted] (59).

Eosinophilia

Eosinophil count increase was observed in [redacted] in the delayed treatment arm and [redacted] in the bulevirtide 10 mg treatment arm, while eosinophilia was reported across [redacted] in the bulevirtide 2 mg group ([redacted]) and the bulevirtide 10 mg group ([redacted]). All eosinophilia AEs were Grade 1 in severity, and none resulted in discontinuation of the study drug (59).

Injection site reactions

At Week 48, injection site reaction AEs were experienced by [redacted] subjects ([redacted]) in the bulevirtide 2 mg treatment group and [redacted] subjects ([redacted])

subjects in the bulevirtide 10 mg treatment group. The higher proportion with injection site reactions in the bulevirtide 10 mg treatment group is likely related to the additional daily injection required to receive this dosage. All injection site reaction AEs were Grade 1 or Grade 2 in severity, and none resulted in the discontinuation of the study drug (59).

Skin and subcutaneous disorders

Skin and subcutaneous disorder AEs were experienced in [redacted] participants ([redacted]) in the bulevirtide 2 mg treatment group, and in [redacted] subjects ([redacted]) in the bulevirtide 10 mg treatment group. Only [redacted] participants ([redacted]) in the delayed treatment arm reported a skin and subcutaneous disorder AE. All AEs were Grade 1 or Grade 2 in severity, and none resulted in the discontinuation of the study drug.

B.2.10.1.5 Study drug discontinuation

No TEAEs led to the discontinuation of the study drug (59).

B.2.10.1.6 Deaths

There were no deaths in MYR 301 as of the 48 week data cut-off (59).

B.2.10.2 MYR 202

The safety and tolerability of bulevirtide for the treatment of adults with CHD was evaluated as a secondary outcome in MYR 202. The SAS was defined as all patients who received at least one dose of bulevirtide. AEs were coded with MedDRA version 21.0 (58).

A total of 118 subjects were enrolled for the Phase 2 MYR 202 study, of which 90 subjects received at least one dose of bulevirtide (see Figure 8). At least one injection interruption was observed in 20 of 90 (22.2%) subjects, with 4 of 28 (14.3%) participants the bulevirtide 2 mg treatment arm experiencing injection interruptions, followed by 9 of 32 (28.1%) participants in the bulevirtide 5 mg group and 7 of 30 (23.3%) subjects in the bulevirtide 10 mg treatment arm. Despite this, all patients were compliant with bulevirtide according to the definition stated in the study protocol

(unsatisfactory compliance was defined as missed study drug doses for three consecutive days or four missed doses over 28 days). In accordance with the treatment regimen specified in study design of MYR 202 (see Section B.2.3.2.2), the mean number of weeks of treatment with bulevirtide was 24.18 weeks (range: 18.9 – 36.7 weeks), while the mean duration of TDF exposure was 54.51 weeks (range: 18.9 – 61.6 weeks) in the three bulevirtide treatment groups (58).

B.2.10.2.1 Summary of adverse events

In total, 406 AEs were reported in 76 of 118 (64.4%) subjects in the MYR 202 study (Table 31). Most AEs were reported within the system organ class investigations, blood and lymphatic system disorders, general disorders and administration site conditions, and gastrointestinal disorders. The most common AEs (past conditions) were total bile acids increased, ALT increased, and AST increased (Table 32). Most AEs were of mild (Grade 1) to moderate (Grade 2) intensity, with only 23 AEs assessed as severe (Grade 3). There were no deaths recorded in the study (58).

Compared to TDF alone, there were more treatment-emergent AEs reported for participants receiving bulevirtide in all intervention groups and the number of AEs increased with increasing bulevirtide dose.

Table 31: Overview of AEs (SAS; MYR 202)

	BLV 2 mg + TDF (n=28)	BLV 5 mg + TDF (n=32)	BLV 10 mg + TDF (n=30)	TDF (n=28)	Total: n=118
Any AE, n (%)	18 (64.3)	21 (65.6)	23 (76.7)	14 (50.0)	76 (64.4)
Any SAE, n (%)	0 (0.0)	3 (9.4)	2 (6.7)	1 (3.6)	6 (5.1)
Any AE leading to withdrawal, n (%)	0 (0.0)	1 (3.1)	0 (0.0)	1 (3.5)	2 (1.7)
Any AE leading to death, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AEs by severity					
Mild	16 (57.1)	19 (59.4)	22 (73.3)	13 (46.4)	70 (59.3)
Moderate	5 (17.9)	14 (43.8)	10 (33.3)	6 (21.4)	35 (29.7)
Severe	3 (10.7)	4 (12.5)	3 (10.0)	1 (3.6)	11 (9.3)

AEs by causality					
Not related	12 (42.9)	16 (50.0)	15 (50.0)	14 (50.0)	57 (48.3)
Related	12 (42.9)	17 (53.1)	22 (73.3)	0 (0.0)	51 (43.2)

Key: AE: adverse event; BLV: bulevirtide; TDF: tenofovir; SAE: serious adverse event; SAS: safety analysis set.
Notes: Percentages are based on the number of participants within each treatment group.
Source: Table 43, MYR 202 CSR (58).

B.2.10.2.2 Common adverse events

AEs that occurred in ≥10% of patients in any treatment group in the SAS are summarised below in Table 32. The most common AE reported across all the bulevirtide treatment groups was an increased in total bile acids (58). As highlighted in Section B.2.10.1, bile salt elevations are mechanistically due to the binding of the NTCP receptor by bulevirtide.

Table 32: Most common AEs reported by subjects treated with bulevirtide (SAS; MYR 202)

	BLV 2 mg + TDF (n=28)	BLV 5 mg + TDF (n=32)	BLV 10 mg + TDF (n=30)	BLV total (n=90)
Subjects with any AE, n (%)	**18 (64.3)**	**21 (65.6)**	**23 (76.7)**	**62 (68.9)**
Total bile acids increased	8 (28.6)	12 (37.5)	15 (50.0)	35 (38.9)
ALT increased	4 (14.3)	7 (21.9)	9 (30.0)	20 (22.2)
AST increased	3 (10.7)	7 (21.9)	8 (26.7)	18 (20.0)
Thrombocytopenia	3 (10.7)	5 (15.6)	2 (6.7)	10 (11.1)
Fatigue	1 (3.6)	2 (6.3)	5 (16.7)	8 (8.9)
Nausea	1 (3.6)	4 (12.5)	3 (10.0)	8 (8.9)
Neutropenia	1 (3.6)	4 (12.5)	0 (0.0)	5 (5.6)
Dizziness	2 (7.1)	2 (6.3)	3 (10.0)	7 (7.8)q
Headache	2 (7.1)	2 (6.3)	3 (10.0)	7 (7.8)
Leukopenia	4 (14.3)	2 (6.3)	0 (0.0)	6 (6.7)
Lymphopenia	3 (10.7)	0 (0.0)	0 (0.0)	3 (3.3)

Key: AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; SAS: safety analysis set.
Notes: Percentages are based on the number of participants treated with bulevirtide.
Source: Table 45, MYR 202 CSR (58).

B.2.10.2.3 Summary of serious adverse events

No SAEs were reported in the bulevirtide 2 mg + TDF treatment arm. One patient reported hepatic cirrhosis in the TDF monotherapy group, which was judged to be related to progression of the underlying disease (58).

B.2.10.2.4 Study drug continuation

Study drug discontinuation due to an AE was reported in one subject in the bulevirtide 5 mg treatment arm. The patient withdrew from the study and required hospitalisation after experiencing anaemia, which was judged as not related to bulevirtide. This SAE was assessed as life-threatening and was not resolved when the patient discontinued from the study (58).

B.2.10.2.5 Deaths

There were no deaths in the study (58).

B.2.11 Ongoing studies

MYR 301 is the pivotal trial for the treatment of CHD. Whilst the primary endpoint is based on interim 48-week data, an interim 96-week data cut is expected to be made available in [redacted]. Depending on the timing of availability, this may be available to be submitted as new evidence during this technology appraisal which is expected to provide further evidence as to the optimal time to assess treatment response and demonstrate the continued benefits of ongoing treatment with bulevirtide over the longer-term.

In addition, the ongoing MYR 204 study is exploring the combination of PEG-IFN and bulevirtide as a potentially curative treatment option for patients with hepatitis delta (110).

B.2.12 Interpretation of clinical effectiveness and safety evidence

Bulevirtide is a novel, first-in-disease and first-in-class entry inhibitor used to treat CHD. Bulevirtide mimics the NTCP-binding domain, thereby selectively binding and inactivating NTCP, preventing HDV entry into host cells (1,2). In November 2021,

bulevirtide received conditional marketing authorisation from the MHRA for the treatment of CHD in adults with compensated liver disease (8).

As the first approved treatment for HDV in Europe, clinical experts considered bulevirtide to be a step change in the treatment of CHD (31). Bulevirtide is designated as an orphan medication by the EMA and has also received PIM designation by the MHRA (26). Furthermore, experts consulted during the development of the EPAR agreed that there is an unmet medical need for bulevirtide, and that chronic HDV infected, or HDV-RNA positive adult patients with compensated liver cirrhosis would constitute a patient population in urgent need of treatment (3).

Bulevirtide specifically blocks viral entry by binding to NTCP, and as such, does not interfere with HDV viral replication or hepatocyte egress of the virus. Because of this, the observed declines in plasma HDV RNA during treatment with bulevirtide reflect a decline in the number of infected, virus-producing hepatocytes in the liver. By blocking the essential entry receptor, the *de novo* infection of liver cells is decreased, viral spread is inhibited, and the lifecycle of HDV is disrupted (111). This event is expected to lead to both reduced necroinflammation and HDV viral load decline by the same mechanism of prevention of new infections (59).

The efficacy and safety of bulevirtide in participants with CHD was investigated in the multicentre, open-label, randomised pivotal Phase 3 MYR 301 trial, as well as the supporting MYR 202 trial.

The MYR 301 population represented a group with particularly poor prognosis, with [redacted] of patients cirrhotic at baseline, and [redacted] having failed prior treatment with IFN-based therapy (59). Clinical experts suggested that the baseline characteristics observed were generalisable to patients currently seen in UK clinical practice (31). However, in a 2020 retrospective study by Spaan *et al*. found a lower median age of 36.0 years, a more relevant figure compared to MYR 301 based on study sites (78).

Overall, [redacted] of patients in the bulevirtide 2 mg treatment group achieved a combined response at Week 48, compared to just [redacted] in the delayed treatment arm

([redacted]) (59). Data from previous studies suggests that patients achieving undetectable HDV RNA or a ≥2-log_{10} decline in HDV RNA levels, and ALT normalisation, are at a reduced risk of developing complications of liver disease, such as HCC, cirrhosis, decompensation, and death (20,35,36,61).

The consensus from the 2019 EASL-AASLD Conference was that a decrease in HDV RNA by ≥2-log_{10} IU/mL from baseline might suffice as a primary endpoint for clinical trials for a maintenance treatment for CHD (25). However, alongside an improvement in virologic response, primary endpoints used to predict a clinical benefit in people with CHD should also provide an improvement in associated liver inflammation evident by a biochemical response. Therefore, as recommended by the FDA (53), a combined response was used as the primary endpoint for the MYR 301 study. The combined response composite endpoint sets a high bar for level of response, given it requires the fulfilment of two surrogate outcomes, one of which is a non-specific marker of liver inflammation. When analysing the individual components of the combined response, [redacted] of patients in the bulevirtide 2 mg treatment group achieved undetectable HDV RNA or a ≥2-log_{10} decline in HDV RNA levels at Week 48, compared to just [redacted] in the delayed treatment arm ([redacted]) (59).

With regards to ALT normalisation, [redacted] of subjects achieved normal ALT levels at Week 48, compared to [redacted] in the delayed treatment arm (59). Furthermore, as shown in Appendix N, for patients who demonstrated a significant reduction in HDV RNA, but failed to achieve the combined endpoint, [redacted] (107). By also taking into account the innovative mechanism of action of bulevirtide, whereby uninfected and newly formed hepatocytes are protected from new and re-infection, the proportion of responders is predicted to increase further beyond Week 48. In this regard, data collection is still ongoing with MYR 301, with 96-week data expected to become available in [redacted].

Furthermore, at Week 48, the FibroScan® measurement of liver stiffness indicated that the bulevirtide 2 mg ([redacted] kPa) group had a significant decrease in liver stiffness from baseline compared to the delayed treatment group ([redacted] kPa) (59). In addition, an exploratory substudy of MYR 301 found that there was a strong correlation between HDV RNA and HDAg levels, which demonstrates that the number of infected hepatocytes reduced (80). As established by Farci *et al*. (2004), there is an association between fibrosis regression and a significant decrease in HDV viral load (103), which would suggest that patients responding to bulevirtide could experience an improvement in fibrosis and cirrhosis.

A multicentre, open-label, randomised supporting Phase 2 MYR 202 study further supports the efficacy and safety of bulevirtide, albeit over a shorter 24-week treatment period. Similar to MYR 301, the MYR 202 population represented a group with a poor prognosis, with 50.0% of patients cirrhotic at baseline, and 56.8% having failed prior therapy with IFN-based therapy (58).

The MYR 202 study assessed the efficacy and safety of bulevirtide in suppressing HDV replication in adults with CHD, in combination with TDF, over a shorter 24-week treatment period. The trial achieved its primary endpoint of an HDV RNA response at Week 24, which was observed in 53.6% of participants treated with bulevirtide 2 mg + TDF, compared to 3.6% of participants receiving TDF alone. Furthermore, treatment with bulevirtide 2 mg + TDF was associated with a statistically significantly higher proportion of participants achieving a combined response at Week 24 compared to TDF monotherapy (58).

In summary, bulevirtide has demonstrated unprecedented efficacy in a population of adults with CHD with compensated liver disease. Evidence from the MYR 301 and MYR 202 clinical studies demonstrates that treatment with bulevirtide results in a greater proportion of individuals achieving a combined response, HDV RNA decline or suppression, and ALT normalisation, compared to BSC or delayed treatment. The proposed population highlighted in the decision problem currently has no existing treatment options. Thus, as the only approved treatment for CHD, bulevirtide represents an important therapeutic option to address the rapid progression of the

disease in this population, and reduce the risk of developing severe liver-related complications including cirrhosis, HCC, decompensation and death.

B.2.12.1 Strengths and limitations of the evidence base

Although HDV is the most severe form of viral hepatitis (10), no studies have been identified that provide utility values with HDV. The effect of bulevirtide on the HRQoL of people with HDV was assessed using EQ-5D-3L in the Phase 3 MYR 301 clinical study (see Section B.2.6.1). Baseline EQ-5D-3L scores did not differ between patients with and without liver cirrhosis, with a mean score of [redacted] for non-cirrhotic patients and a score of [redacted] for cirrhotic subjects. Clinical experts confirmed a difference of [redacted] was an unexpected result (31). Furthermore, these findings are inconsistent with previous research which suggests that cirrhosis status in chronic hepatitis infection, including HBV monoinfection, negatively impacts patient QoL (104–106). As a result, base-case health state utilities are sourced from a meta-analysis of hepatitis B, and a statistical analysis of MYR 301 data.

Whilst it is acknowledged that the sample size for the Phase 3 MYR 301 study could be deemed small, CHD is considered to be an orphan disease in Europe (7). Due to difficulties in hepatitis delta screening and diagnosis, clinical studies of hepatitis delta often suffer from small sample sizes, which can make collecting statistically significant results for clinical outcomes challenging. MYR 301 represents the largest CHD clinical study to-date, with a larger population of patients recruited in comparison to the multicentre HIDIT-I and HIDIT-II studies used to investigate the efficacy and safety of PEG-IFN for CHD (76,112). Furthermore, despite an acknowledgement of a small trial population, the EMA granted bulevirtide conditional marketing authorisation given the beneficial effect demonstrated by the available data, and in light of the limited treatment options and critical unmet needs associated with the disease (3).

Long-term liver disease complications of hepatitis delta are impractical targets for clinical trials, as they require a large number of participants followed for an extended period of time to demonstrate a clinical benefit (52). As a result, clinical trials for treatments for hepatitis rely on virologic and biochemical endpoints as surrogate

markers that are likely to predict clinical benefit in people with CHD. According to the FDA's guidance on developing treatments for CHD, and discussion from the 2019 EASL-AASLD Conference, surrogate endpoints should provide evidence for both a decline in virologic replication, and an improvement in associated liver inflammation evident by a biochemical response (25,53). The main surrogate endpoint used to predict clinical benefit, as recommended by the FDA, is combined response, or 'the proportion of trial patients with undetectable serum HDV RNA (defined as undetectable HDV RNA [HDV RNA <LoD, where LoD=6 IU/mL] or decrease in HDV RNA by ≥2-$\log_{10}$ IU/mL from baseline) and ALT normalisation' (53).

Data from the MYR 301 and MYR 202 studies shows a higher proportion of subjects treated with bulevirtide 2 mg demonstrated a combined response compared to BSC. As mentioned previously in this section, the consensus from the 2019 EASL-AASLD Conference was that decline in HDV RNA by ≥2-$\log_{10}$ IU/mL from baseline might suffice as a primary endpoint for clinical trials for a maintenance treatment for CHD (25). The use of a combined response as a primary endpoint, as recommended by the FDA (53), provides a more stringent definition of a responder, and subsequently makes this endpoint more difficult to achieve. Given the aforementioned difficulties in demonstrating an improvement in long-term liver disease complications in a clinical trial setting, a combined response represents a high bar for treatment efficacy.

B.2.12.2 Applicability of clinical evidence to practice

B.2.12.2.1 Patient characteristics

The population of MYR 301 represents a mixture of treatment naïve and experienced patients, with [redacted] of patients having received prior therapy with IFN-based therapy. A similar rate of prior treatment with IFN-based therapy was observed in MYR 202 (56.8%). NICE guidelines recommend a trial of PEG-IFN for the treatment of adults with CHD (72). Feedback from clinical experts also suggests that most patients diagnosed with HDV have already tried IFN-based therapy, owing to a lack of other options (31). Therefore, prior use of IFN-based therapy in MYR 301 can be considered representative of UK clinical practice.

Although neither of the relevant clinical studies included any UK study centres, there were study sites in Russia, Germany, Italy, and Sweden. Over half of patients (57%) in the pivotal MYR 301 study were recruited from Russia. EASL guidelines for the treatment of hepatitis B are considered to follow the rules of good clinical practice in Russia, and thus the treatment and management of CHD is likely to be aligned to UK clinical practice (see Section B.1.3.3).

While ALT normalisation was defined as ALT ≤ ULN by central laboratory, the cut-off value for the ULN was higher in Russia than the other participating countries, as outlined below:

- Russia: ≤31 U/L for females and ≤ 41 U/L for males.
- Others (Germany, Italy, and Sweden): ≤34 U/L for females and ≤ 49 U/L for males.

The EASL guidelines use a traditional cut-off value for the ULN at approximately 40 U/L (27). The definition adopted by Russia is more stringent and requires a greater decline in ALT levels in order to achieve the combined response endpoint. EASL guidelines are expected to be followed for the treatment and management of patients with CHD in Germany, Italy, and Sweden, which collectively contributed to almost half of the patients recruited for the pivotal MYR 301 clinical study.

Overall, as described in Section B.2.3.1, clinical experts generally agreed that the baseline characteristics of MYR 301 were reflective of the patients they expect to treat in clinical practice (31). However, in a 2020 retrospective study by Spaan *et al*. found a lower median age of 36.0 years, compared to the median age of years observed in the MYR 301 study (78). Given this data is UK specific, it can be considered a more appropriate figure for clinical practice.

B.2.12.2.2 Analysis sets

In consideration of the most appropriate analysis set for decision making, the FAS for MYR 301 (n = 150) is presented and the data for bulevirtide 2 mg and delayed

treatment is used in the subsequent cost-effectiveness analysis. This analysis set includes all treated patients in the pivotal MYR 301 study.

B.2.12.2.3 Service provision

Treatment with bulevirtide should be initiated by a physician experienced in treating patients with HDV. Appropriate training should be given to the patients self-administering the product to minimise the risk of the injection site reactions when injecting bulevirtide at home. No additional infrastructure or personnel is required, and therefore bulevirtide would fit in with current service provisions already set up within NHS England.

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

An SLR was conducted to identify published cost-effectiveness analyses for bulevirtide or BSC for the treatment of CHD. The SLR methods are detailed in Appendix G. The identified studies are summarised in Table 33.

Table 33: Summary list of published cost-effectiveness studies

Study	Year	Summary of model	Patient population (average age in years)	Intervention/comparator	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Frolov et al., 2020 (113)	2020	Excel based model	CHD participant of MYR 203 clinical trial with mean age of 37.6 years	Bulevirtide/PEG-IFN	Bulevirtide: 53 PG-IFN: 13*	Bulevirtide: 1,818,432.00 rubles PG-IFN: 403,644.00 rubles	326,050*
Goyal and Murray 2016 (70)	2015	Markov model was used to evaluate the economic and health outcomes. The basic structure of our extended model was derived from Wu et al. 2010 and 2012. The extended model included three different classes of infections: HBeAg (+) CHB, HBeAg (-) CHB, and HBeAg (-) CHD. Eight mutually exclusive states including chronic stage with no additional aspects (CSB or CSD), VR after therapy, SVR after therapy, CC, DC, HCC, LT, and Post-LT	Hypothetical Chinese cohort of 10,000 individuals aged 30–60 years	PEG-IFN/ IFN, Oral Nucleoside, Palliative care	PEG-IFN: 1.56 (10^5) IFN: 1.23 (10^5) Entecavir: 1.48 (10^5) Telbivudine: 1.41 (10^5) Adefovir: 1.30 (10^5) Lamivudine: 1.34 (10^5) Palliative care: 0.74 (10^5)	PEG-IFN: 3.34 (108) US$ IFN: 2.83 (108) US$ Entecavir: 2.16 (108) US$ Telbivudine: 2.10 (108) US$ Adefovir: 2.38 (108) US$ Lamivudine: 2.14 (108) US$ Palliative care: 2.39 (108) US$	PEG-IFN: 1148.7 IFN: 884.2 Entecavir: -316.6 Telbivudine: -442.7 Adefovir: -196.5 Lamivudine: -418.2

Ouared et al., 2020 (113)	NR	An existing Hepatitis C Markov model was adapted. Natural history of HDV was simulated through fibrosis progression, CC, DC, HCC and LT	NR	PEG-IFN/-	11.55 Based on transition probability calibration: 9.7 (8.8 – 10.2)	€51,035 Based on transition probability calibration: €42,318 (€38,067-€49,532)	-

*Study reported efficacy in terms of 'combined response rate'

Abbreviations: QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio; CC, Compensated Cirrhosis; DC, Decompensated Cirrhosis; HCC, Hepatocellular Carcinoma; LT, Liver Transplantation; PEG-IFN, Pegylated interferon; SVR, Sustained Virologic Response; VR, Virologic Resistance.

B.3.2 Economic analysis

The SLR of published cost-effectiveness studies identified that none of the studies addresses the decision problem presented in section B.1.1. A *de novo* cost-effectiveness model was therefore developed to appraise the cost-effectiveness of bulevirtide as per the scope of this submission.

B.3.2.1 Patient population

The patient population included in the economic evaluation is defined as: adults with CHD who have compensated liver disease and evidence of significant fibrosis (METAVIR stage greater than or equal to F2), whose disease has responded inadequately to IFN-based therapy, or who are ineligible to receive IFN-based therapy due to intolerance or contraindication.

As discussed in Section B.1.1, the patient population included in the economic evaluation is different from the final scope issued by NICE and is narrower that the marketing authorization for bulevirtide.

B.3.2.2 Model structure

The cost-effectiveness model takes the form of a short-term decision tree for the first 72 weeks of treatment, followed by a Markov cohort model that follows patients through the lifetime of their disease. The Markov structure is presented in Figure 17. The model structure is similar to well established nature history models of HBV which have been adopted for previous economic evaluations of treatments of chronic HBV (TA173 (115), TA153 (115), TA154 (115), TA96 (115)) and more recently in other anti-viral treatments for chronic HCV (TA507 (116), TA499 (115)). The model structure was validated by an expert advisory board comprising clinical and health economic experts held in November 2021.

At baseline, patients are distributed across fibrosis stages and are assigned to treatment (bulevirtide or BSC). In the decision tree portion of the model, there are two efficacy assessments/continuation rules at Weeks 48 and 72 of treatment that determine whether the patient remains on treatment. The Week 48 assessment can

be considered an early assessment of efficacy that evaluates achievement of a virologic (HDV-RNA undetectability or ≥2-log_{10} decline) while the Week 72 assessment can be considered a definitive assessment of both virologic and biochemical response (MYR 301 primary endpoint; composite response of HDV-RNA undetectability or 2-log_{10} decline and ALT normalisation). Having these two continuation rules allows sufficient time for patients to achieve a clinical response (response rate was still increasing at Week 48 in MYR 301) while ensuring that patients who are not responding adequately to treatment do not incur ongoing treatment costs. This approach is also consistent with the current NICE guideline for assessment of response to PEG-IFN which states "*Consider stopping peginterferon alfa-2a if there is no decrease in HDV RNA after 6 months to 1 year of treatment. Otherwise, continue treatment and re-evaluate treatment response annually*"(72). Week 72 was considered appropriate as a final assessment timepoint based on extrapolations of the composite responder rate beyond 48 weeks which anticipate a peak at around 72 weeks (see section B.3.3.2).

Patients who fail to achieve virologic response at Week 48 are considered non-responders and discontinue treatment. Those remaining on treatment are split into complete responders (patients who achieve both a virologic and biochemical response according to the MYR 301 primary endpoint) and partial responders (those who achieve a virologic response only). At Week 72, patients who fail to achieve a biochemical response are assumed to discontinue treatment leaving only complete responders on treatment going forwards. This can be considered a conservative approach, given that post-hoc analyses have shown that a large majority of patients who do not achieve the combined response primary endpoint have ALT within 1-2x ULN at Week 48 and are likely to have a significant clinical benefit (see Figure 29, Appendix N).

Patients progress through stages of fibrosis before developing cirrhosis. Cirrhotic patients remain asymptomatic or with limited symptoms (i.e. CC) before developing DCC. As chronic infection progresses, patients are at higher risk of developing HCC. Over the course of a simulation process, patients can achieve spontaneous or treatment-induced virologic responses (e.g., HBsAg seroconversion or HDV

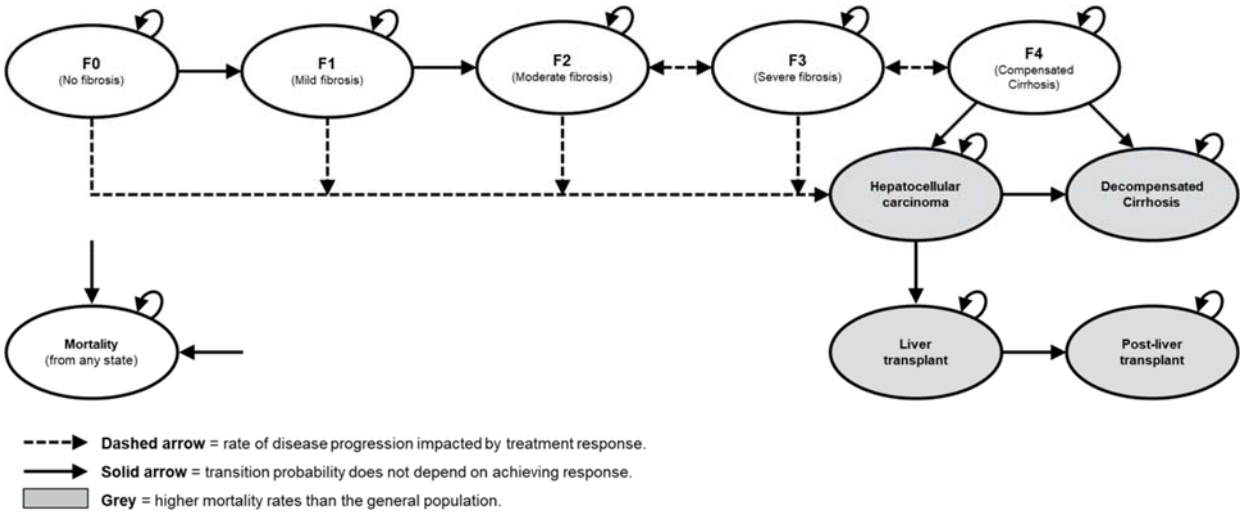
combined response endpoint) or develop liver complications (e.g. CC, DCC, HCC, or LT).

The model links the treatment response definitions to the slowing or stopping of disease progression. The MYR 301 combined response endpoint of HDV-RNA undetectability or ≥2-log_{10} decline and ALT normalisation (defined in the economic evaluation as complete responder) was linked to HDV disease management by assuming that a combination of improvement on virologic and inflammation biomarkers halts disease progression, leading to a reduction in HDV-related morbidity, mortality, healthcare resource utilisation (HCRU), costs and improvement in patient quality of life. It is assumed that achievement of biochemical response, i.e. ALT normalisation in addition to virologic response (defined as complete response in the economic evaluation) indicates that the liver is not showing any signs of inflammation and thus no disease progression would occur. The MYR 301 virologic response endpoint of HDV-RNA undetectability or ≥2-log_{10} decline (defined as partial responder in the economic evaluation) was linked to HDV disease management by assuming that an improvement on virologic biomarkers without ALT normalisation slows (but does not halt) disease progression (38).

Health state transitions for both responders and non-responders are illustrated in Figure 17. Complete responders can progress through stages F0 – F4 or regress from F4 to F3 or from F3-F2. Partial responders and non-responders can progress through F0-F4, but not regress. As with HBV, from all fibrosis stages, non-responders can develop HCC. However, from CC (fibrosis stage 4 [F4]), both responders and non-responders can develop HCC or DCC. From the DCC state, patients may then move to the HCC state. Patients in the HCC state may undergo LT. There is a mortality risk associated with LT that may be due to either death during the operation or following the operation, or due to complications such as graft rejection. Patients who do not die due to LT within one year move to the post-liver transplant (PLT) state. For both responders and non-responders, beginning in F4 (CC), patients may transition to liver-related mortality at any time. While transitions between responders and non-responders are similar, responder patients progress slower than non-responders. As noted above, however, complete responders can

also regress from F4 (CC) to F3 and from F3 to F2 while on treatment. This possibility to regress is established based on expert opinion and fibrosis regression observed in HBV mono-infected patients who are virologically supressed on HBV-treatment (103), (102). A summary of the definitions of responder, continuation rules and assumptions regarding disease progression is presented in Table 34.

Figure 17: Model structure



Key: F0: fibrosis stage 0; F1: fibrosis stage 1; F2: fibrosis stage 2; F3: fibrosis stage 3; F4: fibrosis state 4 (compensated cirrhosis).

The analysis was conducted from the perspective of the NHS and personal social services in England and Wales, in line with current NICE guidelines (114). The base-case analysis thus considers only direct healthcare costs. Costs and outcomes are discounted at an annual rate of 3.5%, in line with the NICE reference case (114). Table 35 presents additional features of the current economic analysis and compares them to previous relevant NICE technology evaluations in CHB.

Table 34: Summary of clinical assumptions in model

Type of responder	Definition	Impact on progression/regression.	Continuation rule
Complete responder	Composite response (HDV-RNA undetectability or ≥2-$\log_{10}$ IU/ml decline and ALT normalisation)	Virtually halts progression. Some patients regress from F4 (CC) to F3 and from F3 to F2	None
Partial responder	Virologic response (HDV-RNA undetectability or 2-$\log_{10}$ decline)	Slows progression	Discontinue treatment at 72 weeks
Non-responder	Do not achieve either virologic (HDV-RNA undetectability or 2-$\log_{10}$ decline or biochemical response	No impact on progression	Discontinue treatment at 48 weeks

Table 35: Features of the economic analysis

	Previous evaluations			Current evaluation	
Factor	**TA153 - Entecavir for the treatment of chronic hepatitis B**	**TA173 - Tenofovir disoproxil for the treatment of chronic hepatitis B**	**TA154 - Telbivudine for the treatment of chronic hepatitis B**	**Chosen values**	**Justification**
Time horizon	Lifetime	Lifetime	Lifetime	Lifetime	Long enough to capture differences in costs and outcomes between the technologies being compared, in line with the reference case (114). The time horizon has been chosen considering the cohort mean age of 40.2 years at baseline.
Treatment waning effect	Not applied	Not applied	Not applied	Not applied	Lack of data to support a treatment waning effect.
Source of utilities	Levy et al. (2007) (116). Standard gamble utilities were elicited using an interviewer-administered survey from populations in	Ossa et al., 2005 (116), a UK preference-elicitation study of hepatitis B-related health states in infected and	Health state valuations were sourced from Shepherd et al., 2006 (117).	Meta-analysis of EQ-5D-3L utility values in HBV. Incremental EQ-5D-3L utility of responder from an	In the absence of HDV-specific utility values, clinicians felt that HBV quality of life was the most generalisable proxy condition (as

	six countries with a total number of 534 CHB-infected patients and a total number of 600 uninfected respondents. The age-sex adjusted utility values elicited from 100 uninfected respondents in the UK were used in the model.	uninfected persons. Standard gamble utility weights for six disease-related health states were elicited from a sample of 100 uninfected persons and 87 patients chronically infected with HBV in the UK. Utilities applied in the model were those from the infected population only.		analysis of MYR 301.	opposed to HCV). The cost-effectiveness model has been supplemented with data from MYR 301 as this is the key clinical study of Bulevirtide to demonstrate utility gain of responders.
Source of costs	Health state costs were taken from Shepherd et al., 2006 (117). Unit costs for medications were sourced from British National Formulary (BNF).	For the less severe disease states (HBeAg seroconverted, HBsAg seroconverted, active CHB and viral suppression), micro-costing was undertaken based on expert opinion, resource use estimates from Shepherd et al., 2006 (117). For the more severe disease states (compensated	Health state costs were taken from Shepherd et al., 2006 (117). Drug costs were sourced from the BNF. Non–drug costs for patients receiving anti-viral treatment were derived using treatment protocols reported Shepherd et al., 2006 (117).	Health state costs are sourced from Shepherd et al., 2006 (117) and Singh and Longworth, 2017 (118)Unit costs are sourced from NHS reference costs and the BNF.	In the absence of resource use data from HDV patients, data from HBV patients was deemed the most appropriate source given that HDV patients are co-infected with HBV.

		cirrhosis, decompensated cirrhosis, HCC, liver transplant and post-liver transplant), costs were based on large UK costing studies on hepatitis C (117), (117). Unit costs were sourced from the PSSRU, drug tariffs, hospital tariffs and Shepherd et al., 2006 (117).			

B.3.2.3 Intervention technology and comparators

The modelled intervention is Bulevirtide 2 mg once daily, as per its conditional marketing authorisation (8). Bulevirtide is an HBV/HDV entry inhibitor that binds and blocks the jointly used NTCP receptor on liver cells. It misdirects HBV and co-infecting HDV to an unproductive pathway and prevents an infection of the cell. The recommended dose and treatment duration of bulevirtide is 2 mg once daily (every 24 hours ± 4 hours) by SC injection as monotherapy or in co-administration with a NA for treatment of underlying HBV infection (8).

The comparator in the cost-effectiveness model is BSC. BSC consists of current clinical practice for HDV patients and includes non-specific treatments and care. BSC is generally defined as symptomatic treatment, alongside treatment for the underlying hepatitis B. The definition of BSC was validated with leading clinicians in the UK.

B.3.3 Clinical parameters and variables

B.3.3.1 Baseline characteristics

None of the patients enrolled into MYR 301 were from the UK, thus baseline characteristics from the trial were not deemed generalisable to the UK population likely to receive bulevirtide. The baseline age and proportion male in the model were informed by a retrospective analysis of 107 patients with HBV/HDV coinfection attending an outpatient clinic in London, England (78). The baseline characteristics for the subgroup of patients with actively replicating HDV detectable HDV RNA and/or anti-HDV-IgM (n=46) were used to inform the model. This resulted in a baseline age of 35.1 years and a proportion of 58.7% males (78).

In line with the proposed positioning of bulevirtide, in patients with compensated liver disease, the model assumes that patients are distributed amongst health states F2-F4 at baseline. In line with the NICE guideline for treatment with PEG-IFN (72), patients in F0-F1 would not be classed as severe enough to receive bulevirtide in clinical practice and thus these patients are not included at baseline. Patients in any of the advanced liver disease health states (DCC, HCC, LT, PLT) would not meet the

eligibility criteria to initiate treatment and thus no patients are assumed to occupy these health states at baseline. A scenario analysis was explored where the baseline population was restricted to those in the F3-F4 health states only.

21 out of the 46 (46%) patients in the actively replicating HDV detectable HDV RNA and/or anti-HDV-IgM subgroup in Spaan et al., 2020 (78) were cirrhotic at baseline. This is used to inform the proportion of CC (F4) patients at baseline. Spaan et al., 2020 (78) did not provide the proportion of patients in the non-cirrhotic fibrosis stages (F0-F3) at baseline, thus the proportion of non-cirrhotic patients (54%) was reweighted using Romeo *et al.,* 2009. Romeo *et al*., 2009 provide a baseline split of patients by fibrosis stage (F0-F4) in a sample of 299 HDV patients (35). The baseline distribution of patients is reported in Table 36. The distribution applied in the scenario analysis where the baseline population is restricted to F3-F4 patients is reported in Table 37.

Table 36: Distribution of patients amongst fibrosis stages, model base-case

Health states	Proportion of patients	Source
F2 (non-cirrhotic)	16.6%	Spaan et al. 2020 (78), reweighted using Romeo et al., 2009 (35)
F3 (non-cirrhotic)	23.6%	
F4 (compensated cirrhosis)	59.8%	

Table 37: Distribution of patients amongst fibrosis stages, scenario analysis

Health states	Proportion of patients	Source
F3 (non-cirrhotic)	28.3%	Spaan et al. 2020 (78), reweighted using Romeo et al., 2009 (35)
F4 (compensated cirrhosis)	71.7%	

B.3.3.2 Clinical efficacy

Trial data

Key efficacy parameters for bulevirtide were sourced from the Phase 3 MYR 301 trial. MYR 301 is an on-going multicentre, open-label, randomised clinical trial assessing the efficacy and safety of bulevirtide in patients with CHD. The primary

objective of the study is 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 CHD in comparison to delayed treatment. Data from the 2 mg arm was used to inform the efficacy of bulevirtide in the model. The delayed treatment arm was used to inform the clinical efficacy of BSC. The MYR 301 data was restricted to the sub-group of patients who were IFN-experienced.

The key efficacy parameter in the model is the proportion of patients achieving combined response, that is virologic response (HDV-RNA undetectability or ≥2-$\log_{10}$ decline) and ALT normalisation. Patients who achieve this endpoint are categorised as 'complete responders' in the model. Patients who achieve virologic response, but fail to meet the ALT normalisation criteria, are defined as partial responders. The response rates for the combined response endpoint, as observed in MYR 301 are reported in Table 38. The modelled response rates applied in the base-case are reported in Table 39.

Table 38: Combined response rates observed in MYR 301, applied in model base-case

	Sample size	Responders	Non-responders	% responders	Lower CI	Upper CI
Bulevirtide 2mg						
Week 24	26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 48		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC						
Week 24	29	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 48		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 39: Bulevirtide and BSC response rates, model base-case

	Proportion of patients, bulevirtide arm	Proportion of patients, BSC arm
Week 24		
Complete Responder	[redacted]	[redacted]
Partial Responder	[redacted]	[redacted]
Non-responder	[redacted]	[redacted]

Week 48		
Complete Responder	[redacted]	[redacted]
Suboptimal Responder	[redacted]	[redacted]
Non-responder	[redacted]	[redacted]

A scenario analysis was conducted where virologic response was selected as the definition of a complete responder. In this scenario, there are no partial responders. The trial outcomes for virologic response are reported in Table 40. The response rates applied in the scenario analysis are reported in Table 41.

Table 40: Virologic response rates observed in MYR 301, applied in scenario analysis

	Sample size	Responders	Non-responders	% responders	Lower CI	Upper CI
Bulevirtide 2mg						
Week 24	26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 48		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC						
Week 24	29	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 48		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 41: Bulevirtide and BSC response rates, model scenario

	Proportion of patients, bulevirtide arm	Proportion of patients, BSC arm
Week 24		
Complete Responder	[redacted]	[redacted]
Suboptimal Responder	[redacted]	[redacted]
Non-responder	[redacted]	[redacted]
Week 48		
Complete Responder	[redacted]	[redacted]
Suboptimal Responder	[redacted]	[redacted]
Non-responder	[redacted]	[redacted]

Extrapolation of trial data

Non-responders are assumed to discontinue treatment at 48 weeks, leaving complete responders and partial responders on treatment. Although the available follow-up data from MYR 301 are limited to 48 weeks, analysis of the individual patient data (IPD) indicates that response rates were still increasing at that timepoint. Therefore, the proportion of complete responders among those remaining on treatment past 48 weeks is expected to increase. The response rates for the 2mg bulevirtide and delayed treatment arms of MYR 301 up until week 48 were therefore extrapolated to estimate treatment response at weeks 72 and 96. This was done using the EMAX function with continuity correction in the R statistical package (119).

EMAX is a non-linear function that is widely used in the areas of dose-response or exposure-/concentration-response modelling. It is characterised by a monotone, concave response shape. Based on visual inspection of the pattern of observed response rates at weeks 4, 8, 16, 24 and 48, within each treatment group of MYR 301, the shape of the response rates was deemed appropriate to be fit with an EMAX function. Using the general property of the EMAX function and the observed data indicated a very good visual fit. The time course of the response rates was modelled separately for individuals by treatment groups, bulevirtide 2mg or delayed treatment. Specifically, a hyperbolic EMAX model was used in order to capture the rapid response rates observed during the earlier timepoints for some endpoints.

Using the treatment group level observed response rates at weeks 4, 8, 16, 24 and 48, a separate set of EMAX functions were estimated for both combined and virologic response. R software (version 4.1.2) was used for this purpose, with the package “DoseFinding” to estimate the response shape with the ‘fitMod’ function used to fit the model. Once the parameters of the response curve for each endpoint and treatment group were determined, the predicted response values at weeks 72 and 96 were derived. As there is no in-built function or option to handle continuity correction within the DoseFinding R package used for the extrapolation, we used an increasing response rate of 0.05% to 0.5% over the 7 visits from week 4 to week 48, when there is at least one 0% response. In such situations, we also added the small additional response to the non-zero response rate, as they should also be scaled up

per the methodology of continuity correction. This overall approach helps us achieve the target of estimating some reasonable predicted values for Week 72 and 96 and is able to determine the upper and lower confidence intervals for response at these timepoints.

The primary limitation of using this method is that the estimated maximum response could become more than 100% over a longer period of follow-up time, particularly for endpoints with high response starting at earlier timepoints. However, this limitation does not impact the predictions over a reasonable follow-up time course, such as 72 or 96 weeks.

Using the EMAX model, we obtained regression parameters for each response endpoint, allowing us to calculate mean response at weeks 72 and 96 using the following equation:

$$e_0 + e_{max}\, d/(ed_{50} + d)$$

The coefficient values from the EMAX model as well as the predicted response rates are provided in Appendix O. Estimates of the mean for all parameters in the equation were estimated from the EMAX model. The d parameter in the equation is substituted with the value of the respective week i.e. 72 or 96. The extrapolated response rates at weeks 72 and 96 for the composite endpoint are reported in Table 42. The respective response rates for the virologic endpoint are reported in Table 43. These response rates are applied to both the bulevirtide and BSC arms in the base-case.

The removal of the MYR 301 extrapolated response rates was explored in a scenario analysis.

Table 42: Bulevirtide and BSC combined response, extrapolated timepoints

	Proportion of patients, bulevirtide arm	**Proportion of patients, BSC arm**
Week 72		
Complete Responder	[redacted]	[redacted]

Suboptimal Responder	[redacted]	[redacted]
Non-responder	[redacted]	[redacted]
Week 96		
Complete Responder	[redacted]	[redacted]
Suboptimal Responder	[redacted]	[redacted]
Non-responder	[redacted]	[redacted]

Table 43: Bulevirtide and BSC virologic response, extrapolated timepoints

	Proportion of patients, bulevirtide arm	**Proportion of patients, BSC arm**
Week 72		
Complete Responder	[redacted]	[redacted]
Suboptimal Responder	[redacted]	[redacted]
Non-responder	[redacted]	[redacted]
Week 96		
Complete Responder	[redacted]	[redacted]
Suboptimal Responder	[redacted]	[redacted]
Non-responder	[redacted]	[redacted]

B.3.3.3 Natural history

For patients who are off-treatment or on BSC, disease progression is modelled through the natural history of HDV-infection. A pragmatic literature search was performed to identify natural history data in HDV. While multiple publications were identified, the data was heterogenous both for the time-period for which the natural history data were evaluated (for example, ranging from 1980s-2010s) and geographic focus. The population sizes 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 deemed appropriate to calculate the natural history HDV progression based on publications comparing disease progression in HDV/HBV co-infected individuals versus treated HBV mono-infected patients. This

approach was validated with clinical experts at an advisory board, 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. Disease transition rates used in the model (with respective sources and calculations) are presented in Table 44 below.

Table 44: Fibrosis and liver disease transition rates

Health State		Annual Transition Probability	24-week model cycle probability	Source
From	To			
Fx	Fx+1 (complete response)	15.1%	7.3%	Papatheodoris et al., 2008 (120) increased by 3x per Da et al., 2019 (120)
	HCC	1.4%	0.6%	Hsu et al.,2002 (121) increased by 2.77x per Alfaiate (44)
CC	DCC	10.7%	5.1%	Dakin (122) increased by 2.2x per Fattovich
	HCC	6.2%	2.9%	Dakin et al., 2010 (122) increased by 2.77x per Alfaiate (44)
	Death	7.3%	3.4%	Fattovich, 2003 (40) increased by 2x per Fattovich et al., 2000 (19)
DCC	HCC	7.8%	3.7%	Dakin et al., 2010 (122) increased by 2.77x per Alfaiate (44)
	LT	1.6%	0.7%	Dakin et al., 2010 (122)
	Death	15.6%	7.5%	Fattovich, 2003 (40)
HCC	LT	1.6%	0.7%	Dakin et al., 2010 (122)
	Death	56.0%	31.5%	
LT	Death	21.0%	10.3%	
PLT	Death	5.7%	2.7%	

The model also takes into consideration an annual rate of HbsAg seroclearance. The rate of HbsAg seroclearance for patients on bulevirtide, as well as spontaneous clearance rate for patients off treatment, is informed by a published meta-analysis and is 1.13% (123). When adjusted to accommodate the 24-week cycle length, this results in a cycle probability of 0.52%. Patients who achieve HbsAg seroclearance are assumed to discontinue HDV treatment.

B.3.3.4 Disease progression

A pragmatic literature review was completed to identify data regarding the MYR 301 combined response endpoint and its impact on disease progression. Farci et al., 2004 (103) established a relationship between a HDV-RNA 2-log_{10} decline and the reduction in risk of mortality. However, the study was not suitable for use in the model as the mortality data is not aligned with progression from any specific health state in the model.

A review of the existing natural history data identified relationships between HDV-RNA undetectability and disease progression (38). Further, there are known relationships between ALT normalisation and disease progression from HBV mono-infection that can be considered for the HDV/HBV co-infection and HBV mono-infection relationship (65).

To provide robust estimates of the impact of HDV RNA undetectability on natural history data in HDV patients, a systematic literature review and meta-analysis was performed. A systematic literature review 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 synthesised in a meta-analysis, where hazard ratios for specific liver disease progression events (i.e., any liver disease event, progression from CC to DCC, CC to HCC, etc.) were determined. The hazard ratios obtained from the meta-analysis are applied to partial (virologic) responders and are reported below. The effect when combined with the natural history transition rates (Table 44) results in disease progression transition rates for patients achieving sub-optimal (virologic) response as summarised in Table 46.

Table 45: Disease progression treatment hazard ratios, suboptimal responders

Health State		Hazard Ratio (Responder vs. Non-Responder)	Source
From	To		
Fx	Fx+1	0.42	Systematic Literature Review and Meta-Analysis
F0-F2	HCC	0.34	
F3	HCC	0.34	
CC (F4)	DCC	0.26	

	HCC	0.34	of HDV Biomarkers (124)
	Death	0.22	

Table 46: Fibrosis and liver disease transition rates amongst sub-optimal responders

Health State		Annual probability	Cycle (24-week) probability
From	To		
Fx	Fx+1	6.61%	3.11%
F0-F2	HCC	0.48%	0.22%
F3	HCC	0.99%	0.46%
CC	DCC	2.91%	1.35%
	HCC	2.19%	1.02%
	Death	1.63%	0.76%

The model assumes that complete responders (those who meet the composite endpoint of MYR 301) have no progression compared to partial or non-responders. The hazard ratios for complete responders are thus set to 0.001 in the model base-case. The effect when combined with the natural history transition rates (Table 44) results in disease progression transition rates for patients achieving combined response as summarised in Table 47.

Table 47: Disease progression treatment hazard ratios, complete responders

Health State		Hazard Ratio (Responder vs. Non-Responder)	Source
From	To		
Fx	Fx+1	0.001	Assumption
F0-F2	HCC	0.001	
F3	HCC	0.001	
CC (F4)	DCC	0.001	
	HCC	0.001	
	Death	0.001	

Table 48: Fibrosis and liver disease transition rates amongst complete responders

Health State		Annual probability	Cycle (24-week) probability
From	To		
Fx	Fx+1	0.02%	0.01%
F0-F2	HCC	0.00%	0.00%
F3	HCC	0.00%	0.00%
CC	DCC	0.01%	0.01%
	HCC	0.01%	0.00%
	Death	0.01%	0.00%

In the absence of data on the reduction of progression from granular non-cirrhotic fibrosis stages (e.g., F0-F3), it was assumed that the hazard ratio from non-cirrhotic to cirrhotic disease was applied to sequential fibrosis stage transitions (e.g., F0 to F1, F1 to F2 and so forth).

B.3.3.5 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 a previous study in HDV patients responding to PEG-IFN therapy, Farci et al., 2004 (103) reported regression in four of six patients with sustained biochemical response. These patients had active cirrhosis in their first three liver biopsies and an absence of fibrosis in their last liver biopsy. The authors concluded that there was an association between fibrosis regression and a significant decrease in HDV viral load (103). Marcellin et al., (2013) (102) also 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 (102). Expert opinion aligned with these findings that patients who respond to therapy and achieve the combined response endpoint could experience an improvement in cirrhosis/fibrosis due to treatment, and regress. The annual transition rates used in the model for fibrosis regression among combined responders are reported in the table below. The impact of removing fibrosis regression in responder patients was explored in a scenario analysis.

Table 49: Fibrosis regression on treatment in responder patients

Health States		Annual Transition Probabilities	24-week cycle probability	Source
From	To			
CC (F4)	NC (F3)	8.8%	4.17%	Farci et al., 2004 (103)
F3	F2	13.3%	6.37%	Marcellin et al., 2013 (102)

B.3.3.6 Treatment discontinuation

Treatment discontinuation is only incorporated for bulevirtide patients as BSC patients are not on active treatment.

Stopping rules

All patients begin treatment at the start of the model when classified according to their fibrosis stages. Treatment stopping rules for bulevirtide patients are the following: no response to treatment by Week 48, responders having HbsAg seroclearance; or, regardless of stage, disease progression. According to the approved SmPC (see Appendix C), "*treatment should be continued as long as associated with clinical benefit*", so responders may continue treatment unless they achieve HbsAg seroclearance or discontinue therapy. Disease progression to DCC, HCC, LT, and PLT health states also results in the end of treatment.

The model thus includes a stopping rule at Week 48 which removes non-responders from active treatment with bulevirtide. Partial responders, who have achieved virologic response but not biochemical response at Week 48, are able to continue treatment until Week 72. If they do not achieve complete (composite) response by Week 72 then they are withdrawn from active treatment with bulevirtide. Discontinuing patients are assumed to be treated with BSC and no subsequent treatment acquisition costs are thus incurred.

Background discontinuation

In addition to treatment withdrawal due to lack of efficacy (response), the model also accounts for treatment withdrawal for any other reasons, based on rates observed in

MYR 301. 1 out of 49 (2.04%) patients in the bulevirtide 2 mg group discontinued treatment in MYR 301. When converted to a 24-week probability, this results in a probability of 1.03% per model cycle.

B.3.3.7 Adverse events

Only moderate to severe adverse events occurring in ≥5% of patients were incorporated into the model. Adverse event rates for the bulevirtide arm were sourced from the 2 mg bulevirtide arm of MYR 301. For the BSC arm, rates were sourced from the delayed treatment arm of MYR 301. The adverse event rates for each arm are reported in the table below. The impact of adverse events is assumed to occur in the first cycle on in the model.

Table 50: Adverse event rates included in the model

Adverse event	Bulevirtide	BSC	Source
Neutropenia	[redacted]	[redacted]	MYR 301 2mg bulevirtide and delayed treatment arms
Thrombocytopenia	[redacted]	[redacted]	
Leukopenia	[redacted]	[redacted]	
Anaemia	[redacted]	[redacted]	
Fatigue	[redacted]	[redacted]	
Bile acid elevation	[redacted]	[redacted]	

B.3.3.8 Mortality

All-cause mortality is applied using a background mortality rate applied to all patients. The background mortality represents the risk of dying of any cause at a given age and is sourced from national life tables sourced from the Office for National Statistics (ONS) (125).

Liver-related excess mortality is applied from the PLT state onwards, to capture the mortality risk associated with severe liver disease. The excess mortality risk for patients in these health states was sourced from published literature and then converted to a 24-week probability of death to accommodate the model cycle length. The probabilities are reported below.

Table 51: Liver-related mortality risk applied in the model

Health State		Annual TP	Cycle TP	Source
From	To			
CC (F4)	Death	7.26%	3.42%	Fattovich, 2003 (40) increased by 2x per Fattovich et al., 2000 (19)
DCC	Death	15.60%	7.53%	Fattovich, 2003 (40)
HCC	Death	56.00%	31.54%	Dakin et al., 2010 (122)
LT	Death	21.00%	10.31%	
Post-LT	Death	5.70%	2.67%	

B.3.4 Measurement and valuation of health effects

Although the EQ-5D-3L was collected in the MYR 301 trial, the trial data was not deemed suitable for use in the model due to a lack of construct and content validity (see section B.3.4.1). Therefore, the core natural history health state utilities in the model, including the utility of non-responders, were obtained from a meta-analysis of the HBV literature (see section B.3.4.3). The model incorporates an incremental utility for complete responders which is derived from a regression analysis of the MYR 301 data.

B.3.4.1 Health-related quality-of-life data from clinical trials

The MYR 301 trial collected HRQoL data using the EQ-5D-3L, the Hepatitis Quality of Life Questionnaire (HQLQ) and the Fatigue Severity Scale at baseline, 24 weeks and 48 weeks. HRQoL data from the EQ-5D-3L is the preferred measure as this is a standardised and validated generic instrument and the preference elicitation is based on a time trade-off algorithm, in line with the NICE reference case (126).

MYR 301 provides the best available dataset for estimating the effect of bulevirtide on HRQoL, that is, the best estimate of the gain in utility associated with a treatment response for CHD patients. Therefore, these data were carefully explored and analysed in detail. Simple descriptive analyses can be subject to bias and so it is typically recommended that regression modelling is undertaken so that other variables can be controlled for (127).

Utility data do not typically meet the assumptions of an ordinary least squares (OLS) regression model. For instance, EQ-5D values may be subject to censoring, clustering, non-linearity, heterogeneity of variance and may be non-normally distributed. Tobit models, on the other hand, are suited and have been extensively used (128) to examine data such as the EQ-5D where the distribution is effectively truncated (the highest score on EQ-5D is 1.0). Tobit regression models were used to explore the data and estimate the gain in utility for treatment responders at week 24 and week. Compared to baseline, moderate gains at week 48 were observed based on the analysis from the Tobit model (Table 52). The estimate for the gain in EQ-5D scores from the Tobit model are applied in the cost effectiveness model, differentiating responders from non-responders in the same health state.

However, the MYR 301 EQ-5D-3L data is not used for the core health state utilities in the base-case and utilities from the literature are used instead (see section B.3.4.3). The trial data was not deemed suitable for use in the model due to a lack of clinical validity. As discussed in Section B.2.6, and shown in Table 53, baseline data from the MYR 301 show that EQ-5D-3L is insensitive to objective differences between cHDV patients, such as patients with or without cirrhosis, which is clinically not plausible and against the large body of evidence in CHB and chronic HCV (74). In clinical practice, the progression of patients with hepatitis through fibrosis stages, cirrhosis and cancer is expected to further decrease their HRQoL.

The results in Table 53 also show the standard deviations around the mean scores which helps to illustrate that the EQ-5D-3L is a somewhat noisy measure in this sample.

Table 52: Regression analysis of 48-week MYR 301 utility values

	OLS regression			Tobit model around median		
	Estimate	**95% CI**	**p-value**	**Estimate**	**95% CI**	**p-value**
Intercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline EQ-5D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Liver Cirrhosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Composite Responder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 53. Mean baseline utility values from the MYR 301 trial, by compensated cirrhosis status

Reference, Location	Study Design	Health state	Utility method used	EQ-5D derived utility weights, mean (SD)
MYR 301, Russia, Germany, Sweden, Italy	Phase 3, open-label randomized trial	NC cHDV	EQ-5D-3L, UK tariff	0.81 (0.150)
		CC cHDV		0.81 (0.188)

Abbreviations: CC, compensated cirrhosis; cHDV, chronic hepatitis D virus; NC, non-cirrhotic; SD, standard deviation; UK, United Kingdom

These findings may be driven by trial-specific factors, particularly low sample size in each health state (approximately 100 patients with usable data at Week 48, less than 50% of which had CC), possible impact of COVID-19 or rapid progression to CC among CHD patients not adequately controlled for. It is also possible that these results are driven by instrument specific factors, such as the EQ-5D-3L being insensitive to objective differences between CHD patients which would explain the lack of utility difference between non-cirrhotic (NC) and CC patients, or EQ-5D-3L not measuring important features of CHD.

The above-described uncertainties and limitations indicate two key issues with the MYR 301 EQ-5D-3L utility estimates:

- Lack of construct validity: No difference in EQ-5D-3L based utilities for NC and CC at baseline which lacks clinical validity and goes against a large body of literature in hepatitis;

- Lack of content validity: CHD causes fatigue, nausea and vomiting as key symptoms and these issues are not reflected in the descriptive system of the EQ-5D-3L so it is possible that they are not well measured. The presence or absence of these important symptoms may have an effect on the utility weights from EQ-5D-3L. Several studies in various diseases reported that EQ-5D-3L does not appropriately reflect differences in fatigue (129) (130).

The MYR 301 values are therefore not applied in the model base-case, but in a scenario analysis. The health-state utility values for the fibrosis stages in this

scenario are reported in Table 54 below. CHB values are applied to all other health states as per the base case.

Table 54: Health state utility values applied for F0-F4 health states, model scenario

Health State	Responder Composite Response Endpoint Achieved	Non-responder Composite Response Endpoint Not Achieved	
	Utility value	Utility value	Source
F0	[redacted]	0.81	MYR 301
F1	[redacted]	0.81	
F2	[redacted]	0.81	
F3	[redacted]	0.81	
F4 (CC)	[redacted]	0.81	

B.3.4.2 Mapping

No mapping was undertaken for this economic evaluation.

B.3.4.3 Health-related quality-of-life studies

An SLR was conducted to identify studies reporting on the HRQoL of patients with CHD. Full details of the methodology and results of included studies are presented in Appendix H.

As described in Section B.3.4.1, the MYR 301 EQ-5D-3L data were not deemed suitable for the base-case health state utilities. No suitable CHD-specific health state utilities were identified in the SLR reported in Appendix H. The use of proxy conditions is feasible if utility values are available for another condition that is deemed to have a similar impact on HRQoL, then those utility values were sometimes assumed representative of the condition of interest. Based on discussions with clinical experts, CHB and chronic HCV were deemed as the most suitable proxies as the three conditions affect the liver, among other organs, have the same transmission modes and similar disease progression paths – although at different velocities. An SLR and meta-analysis of health state utilities in CHB and chronic HCV were conducted. Full details of the meta-analysis methodology are provided separately (131). Clinical experts attending the UK advisory board stated that utilities for CHB patients were more likely to be representative of HDV health

states and thus the base-case health state utilities for non-responders are informed by the CHB meta-analysis. These values are reported in Table 55 (including the previous values for fibrosis states from Table 54). Utilities for responders are from the same source however they include the utility gain associated with response, as estimated by the tobit model median from the MYR 301 EQ-5D-3L utility analysis (Table 52).

The chronic HCV utilities were applied to the health states in a scenario analysis. These values are reported in Table 56.

Patients with more severe stages of disease (DC, HCC or PLT) were not included in MYR 301 and therefore no HRQoL data are available from the trial for these health states. The utilities for these health states were thus also informed by the CHB meta-analysis in the base-case and by the chronic HCV meta-analysis in a scenario analysis.

Table 55: Health state utility values by response status, model base case

Health State	Responder Composite Response Endpoint Achieved	Non-responder Composite Response Endpoint Not Achieved	
	Utility value	Utility value	Source
F0	[redacted]	0.85	Meta-analysis of CHB utilities (131) (non-responder health states) plus incremental utility of a responder (from MYR 301).
F1	[redacted]	0.85	
F2	[redacted]	0.85	
F3	[redacted]	0.85	
F4 (CC)	0.81	0.76	
DCC	0.46	0.46	
HCC	0.52	0.52	
LT	0.57	0.57	
PLT	0.67	0.67	

Table 56: Health state utility values by response status, model scenario

Health State	Responder Composite Response Endpoint Achieved	Non-responder Composite Response Endpoint Not Achieved	
	Utility value	Utility value	Source
F0	[redacted]	0.85	Meta-analysis of chronic HCV utilities (131) (non-responder
F1	[redacted]	0.85	
F2	[redacted]	0.85	
F3	[redacted]	0.85	

F4 (CC)	0.77	0.72	health states) plus incremental utility of a responder (from MYR 301).
DCC	0.70	0.70	
HCC	0.69	0.69	
LT	0.46	0.46	
PLT	0.80	0.80	

B.3.4.4 Adverse reactions

Utility decrements associated with adverse events were incorporated in the cost-effectiveness model by multiplying the utility decrement by the incidence of the adverse event (Table 50) to determine a one-off value, applied in the first cycle of the model.

Table 57: Utility decrements associated with adverse events included in the model

Adverse event	Utility decrement	Source
Neutropenia	0.163	Tolley et al., 2013 (132)
Thrombocytopenia	0.061	Sullivan et al., 2011 (133) (assumed same as 'other blood disease')
Leukopenia	0.061	Sullivan et al., 2006 (assumed same as 'other blood disorders')
Anaemia	0.036	Sullivan et al., 2011 (133)
Fatigue	0.022	Hagwira et al., 2018 (134)
Bile acid elevation	0.000	Assumption of no disutility

Health-related quality-of-life data used in the cost-effectiveness analysis

Table 58: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
F0 – non-responder	0.85	(0.78-0.91)	CHB meta-analysis (131) (Table 55, page 139)	Meta-analysed values from an appropriate disease analogue, approach validated with KOLs
F1 – non-responder	0.85	(0.78-0.91)	CHB meta-analysis (131) (Table 55, page 139)	

F2 – non-responder	0.85	(0.78-0.91)	CHB meta-analysis (131) (Table 55, page 139)	
F3 – non-responder	0.85	(0.78-0.91)	CHB meta-analysis (131) (Table 55, page 139)	
F4 (CC) – non-responder	0.76	(0.65-0.87)	CHB meta-analysis (131) (Table 55, page 139)	
Utility gain for responders	[redacted]	([redacted])	(Table 52, page 136)	Informed by statistical analysis of trial data
DCC	0.46	(0.20, 0.73)	CHB meta-analysis (131) (Table 55, page 139)	Meta-analysed values from an appropriate disease analogue, approach validated with KOLs
HCC	0.52	(0.22, 0.82)	CHB meta-analysis (131) (Table 55, page 139)	
LT	0.57	(0.51, 0.62)	CHB meta-analysis (131) (Table 55, page 139)	
PLT	0.67	(0.62, 0.72)	CHB meta-analysis (131) (Table 55, page 139)	
Adverse event utility decrements				
Neutropenia	0.16	(0.15, 0.18)	Tolley et al., 2013 (132) (Page 140)	As per the literature
Thrombocytopenia	0.06	(0.05, 0.07)	Sullivan et al., 2011 (133) (assumed same as 'other blood disease') (Page 140)	
Leukopenia	0.06	(0.05, 0.07)	(Page 140)	
Anaemia	0.04	(0.03, 0.04)	Sullivan et al., 2011 (133) (Page 140)	
Fatigue	0.02	(0.02, 0.02)	Hagwira et al., 2018 (134) (Page 140)	

Bile acid elevation	0.00		Assumption of no disutility (Page 140)	Assumption

B.3.5 Cost and healthcare resource use identification, measurement and valuation

Details of how relevant cost and healthcare resource data were identified are presented in Appendix I.

B.3.5.1 Intervention and comparators' costs and resource use

B.3.5.1.1 Acquisition costs

The acquisition cost of bulevirtide once the PAS is applied is [redacted] per pack of 30 vials of 2 mg powder for solution for injection. The recommended dose of bulevirtide is 2 mg once daily (every 24 hours ± 4 hours). This results in a cost of [redacted] per 24-week model cycle.

The treatment acquisition costs are reported in Table 59. Bulevirtide is self-administered, thus no drug administration costs are applied. Patients who are allocated to BSC do not receive active drug treatment for CHD and thus there are no drug acquisition costs applied for these patients.

Table 59: Drug acquisition costs applied in the model

	Pack price after PAS	Vials per pack	Cost per vial	Vials used per 24-week cycle	Total cost per 24-week cycle
Bulevirtide	[redacted]	30	[redacted]	168	[redacted]

B.3.5.1.2 Monitoring costs

Monitoring costs refer to the costs of monitoring the patient while they are treated with either Bulevirtide or BSC. The nature and frequency of each type of monitoring resource use was informed by clinical experts (n=3), who were asked to state the type and frequency of NHS activities that would take place each year for HDV patients at treatment initiation, during treatment and when off-treatment. The

frequency of monitoring resource use for bulevirtide patients is presented in Table 60 and in Table 61 for BSC patients.

Unit costs from the 2019/20 National schedule of NHS costs were then attached to the frequency of HCRU to derive total monitoring costs. Unit costs are reported in Table 62.

Table 60: Monitoring resource use for bulevirtide patients

Event	Treatment Initiation (One-off)		During Treatment (Per Year)	
	Non-cirrhotic	Compensated cirrhosis	Non-cirrhotic	Compensated cirrhosis
Hepatologist visit	1	2	3	4
Outpatient visit	1	1	1	2
Fibroscan®	1	1	1	1
Liver biopsy	1	0	0	0
HBV DNA test	1	1	2	2
HDV-RNA test	1	1	2	2
Liver enzyme test	1	2	2	3
Complete blood count	1	2	2	3
TSH test	0	0	0	0
Renal function test	1	2	2	3
Bilirubin Test/GGT/ALP test	1	2	2	3
Ultrasound for HCC screening and surveillance	1	1	2	1
Protime/INR	1	2	1	3
anti-HDV IgG	1	1	0	0
HBsAg	1	1	1	1
HCV Ab	1	1	0	0
HIV Ab	1	1	0	0
Hepatis A IgG	1	1	0	0
Alpha-feto Protein	1	1	2	2

Table 61: Monitoring resource use for BSC patients

Event	Off Treatment (Frequency per year)

	Non-cirrhotic	Compensated cirrhosis
Hepatologist visit	2	2
Outpatient visit	2	2
Fibroscan®	1	1
Liver biopsy	0	0
HBV DNA test	2	2
HDV-RNA test	1	1
Liver enzyme test	2	2
Complete blood count	2	2
TSH test	0	0
Renal function test	2	2
Bilirubin test/GGT/ALP test	2	2
Ultrasound for HCC screening and surveillance	2	2
Protime/INR	1	2
anti-HDV IgG	0	0
HBsAg	1	1
HCV Ab	0	0
HIV Ab	0	0
Hepatis A IgG	0	0
Alpha-feto protein	2	2

Table 62: Monitoring resource use unit costs

Resource use item	Unit cost	Source
Hepatologist visit	£88.20	Non-admitted face-to-face attendance, consultant led hepatology, currency code: WF01C, service code:306. NHS reference costs 2019-20 (135)
Outpatient visit	£88.20	Non-admitted face-to-face attendance, consultant led hepatology, currency code: WF01C, service code:306. NHS reference costs 2019-20 (135)
Fibroscan®	£43.93	Ultrasound elastography, currency code: RD48Z, outpatient imaging, NHS reference costs 2019-20 (135)
Liver biopsy	£43.93	Ultrasound elastography, currency code: RD48Z, outpatient imaging, NHS reference costs 2019-20 (135)
HBV DNA test	£1.20	DAPS04, Clinical biochemistry, NHS reference costs 2019-20 (135)
HDV-RNA test		
Liver enzyme test		
Complete blood count	£2.53	DAPS05, Haematology, NHS reference costs 2019-20 (135)
TSH test	£1.20	DAPS04, Clinical biochemistry, NHS reference costs 2019-20 (135)
Renal function test		

Bilirubin test/GGT/ALP test		
Ultrasound for HCC screening and surveillance	£45.21	Weighted average of codes RD40Z-RD43Z, Ultrasound scan with duration of less than 20 mins or 20 mins and over, with and without contrast, NHS ref costs 2019-20 (135)
Protime/INR	£2.53	DAPS05, Haematology, NHS reference costs 2019-20 (135)
anti-HDV IgG	£1.20	DAPS04, Clinical biochemistry, NHS reference costs 2019-20 (135)
HBsAg		
HCV Ab		
HIV Ab		
Hepatis A IgG		
Alpha-feto protein		

B.3.5.2 Health-state unit costs and resource use

In addition to the monitoring costs, the model also includes health state costs (Table 63). These health state costs are independent of the monitoring costs as these costs are incurred in health states outside of treatment administration and monitoring for HDV. A targeted literature review was undertaken to identify UK health-state costs. No relevant health-state costs could be identified in HDV, thus health-state costs in HBV populations were thus deemed appropriate. The source for all health-state costs aside from LT and PLT is Shephard et al., 2006 (117). Although these costs are not recent, neither the broad SLR in CHD (Appendix I) nor a targeted search of the HEORO database (136) for HBV-specific data returned any relevant, recently-published cost or resource use data. We thus thought it most appropriate to opt for cost estimates from Shephard et al., 2006 (117) as these costs had been applied in previous NICE submissions in HBV (Table 35) and included the same health states as the *de novo* model. For LT and PLT, more recent costs were available from Singh and Longworth, 2017 (118) and these were thus applied in place of the values reported in Shephard et al., 2006 (117).

Health state costs were converted to 24-week costs to accommodate the cycle length. Costs were inflated to 2020 prices using the ONS healthcare index (137).

Health states F0 to F4 (CC) also include the costs of antiviral therapy to treat underlying HBV infection. The proportion of patients receiving NA treatment was

sourced from MYR 301 and is 60% in the base-case. The antiviral treatment cost applied was for tenofovir and the costs and dosage were sourced from the BNF. These costs are reported in Table 64.

Table 63: Health-state costs applied in the model

Health state	Unit cost	Source
F0	£887	CHB health state cost, Shephard et al. 2006 (117), inflated from 2007 values reported in NICE TA153. BNF and MYR 301 antiviral treatment costs
F1	£887	
F2	£887	
F3	£887	
F4	£1,773	Shephard et al. 2006 (117), inflated from 2007 values reported in NICE TA153
Decompensated cirrhosis	£13,445	
Hepatocellular carcinoma	£11,980	
Liver Transplant	£87,796	Singh and Longworth, 2017 (118), inflated from 2012/13 prices
Post-liver transplant	£25,949	

Table 64: HBV antiviral medication costs applied in the model

Dosage	Units per pack	Cost per pack	Cost per unit	Cycle cost	Source
245mg once daily	30	£28.39	£0.95	£158.98	Tenofovir 245mg tablets, BNF, 2022 (138)

B.3.5.3 Adverse reaction unit costs and resource use

Unit costs of adverse events were sourced from the most recent NHS reference costs (2019/2020) (135) and are presented in Table 65. Unit costs were combined with the adverse event rates reported in Table 50 and applied as one-off costs in in the cycle during which the adverse event occurred.

Table 65: Adverse event unit costs

Adverse event	Unit cost	Source
Neutropenia	£332	NHS reference costs 2018/19, weighted average of DC Agranulocytosis (SA35A–E) (135)
Thrombocytopenia	£368	NHS reference costs 2019/20, weighted average of DC thrombocytopenia SA12G-K (135)
Leukopenia	£457	NHS reference costs 2018/19, weighted average of Daycase - Other haematological or Splenic disorders (SA08G-J) (135)
Anaemia	£370	Weighted average NHS reference costs, Daycase for acquired Pure Red Cell Aplasia or Other Aplastic Anaemia (SA01G–SA01K) (135)
Fatigue	£0	Assumption of no cost
Bile acid elevation	£0	Assumption of no cost

B.3.5.4 Miscellaneous unit costs and resource use

Not applicable.

B.3.6 Severity

Bulevirtide meets the criteria for a severity weight. The quality-adjusted life year (QALY) shortfall was calculated using the calculator tool published by Schneider *et al.,* 2021 (139). The source of general population EQ-5D data is Hernandez *et al.,* 2020 (140). The assumptions that are key to severity are population age, gender and the QALYs for the CHD population in the absence of the intervention, that is the total QALYs associated with the BSC. There are no previous NICE technology appraisals that have been conducted in CHD, thus it is not possible to provide a summary list of QALY shortfall from previous evaluations. The total QALYs achieved with BSC were estimated over a lifetime horizon from the cost-effectiveness model and then input into the QALY shortfall calculator. The data used in the QALY shortfall analysis is summarised in Table 66 and Table 68. The disaggregated time in each health state

and the QALYs for each respective health state for BSC patients are reported in Table 67. Based on the QALY shortfall estimates provided in Table 68, bulevirtide meets the criteria for a severity weighting of 1.2. The QALY threshold for this appraisal is thus between £24,000 and £36,000 per QALY.

Table 66: Summary features of QALY shortfall analysis

Factor	Value (reference to appropriate table or figure in submission)	Reference to section in submission
Sex distribution	59% male, 41% female	Section B.3.3.1 Baseline characteristics
Starting age	35	Section B.3.3.1 Baseline characteristics

Table 67: Summary of health state benefits and utility values for QALY shortfall analysis

State	Utility value: mean (standard error)		Undiscounted life years	
	Non-responder	Responder	Non-responder	Responder
F0	0.81	0.86	0.00	0.00
F1	0.81	0.86	0.00	0.00
F2	0.81	0.86	0.92	1.36
F3	0.81	0.86	1.90	1.04
Compensated Cirrhosis (F4)	0.81	0.86	3.50	1.79
Decompensated cirrhosis	0.70	0.70	1.40	0.00
Hepatocellular carcinoma	0.60	0.60	0.56	0.00
Liver Transplant	0.46	0.46	0.01	0.00
Post-liver transplant	0.80	0.80	0.40	0.00

Table 68: Summary of QALY shortfall analysis

Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute QALY shortfall	Proportional QALY shortfall
18.94	[redacted]	[redacted]	[redacted]

B.3.7 Uncertainty

Due to the nature of CHD, which is recognised as an orphan disease in Europe (28), including difficulties in hepatitis delta screening and diagnosis, clinical studies of hepatitis delta often suffer from small sample sizes, which makes collecting statistically significant results for clinical outcomes challenging. The demonstration of the long-term liver disease complications of hepatitis delta are impractical targets for clinical trials in hepatitis delta, as they require a large number of participants followed for an extended period of time to demonstrate a clinical benefit (52). As a result, clinical trials for treatments for hepatitis rely on virologic and biochemical/histological endpoints as surrogate markers that are likely to predict clinical benefit in people with CHD. Furthermore, there is heterogeneity in progression rates in CHD. These factors combined make it difficult to produce high-quality evidence in this disease area. Given the scarcity of evidence in this area, MYR 301represents the best available clinical and safety data to date. Furthermore, the MYR 301 study is ongoing with Week 96 data expected in [redacted] and Week 240 data in [redacted]. Whilst this longer-term data may help resolve some of the uncertainty in this area, given the severity of CHD and the lack of licensed and effective treatment options, there is a high need for bulevirtide.

B.3.9 Summary of base-case analysis inputs and assumptions

Summary of base-case analysis inputs

Please see Table 97 in Appendix M for the summary of input parameters.

Assumptions

Table 69: Assumptions applied in the model

Assumption	Justification
Progression is captured as a relative risk applied to HBV progression rates.	HDV co-infected patients are well documented as having increased progression to HBV mono-infected patients. Given the heterogeneity observed in progression rates across studies, application of relative risks to HBV progression rates was considered a more robust method by clinicians than analysis of individual studies.
Response to treatment can induce regression in liver fibrosis and cirrhosis	The rates of fibrosis regression for patients achieving complete (combined) response were informed by studies conducted in HDV and HBV patients. This approach was validated with clinical experts who stated that patients who respond to therapy and achieve the combined response endpoint could experience an improvement in cirrhosis/fibrosis due to treatment, and regress.
Responders have a small utility gain compared to non-responders in the same health state	This assumption is based on rigorous statistical analysis of the MYR 301 trial data. The utility gain estimate for responders ([redacted]) has been estimated from a tobit regression model, which is well-suited for EQ-5D data.
No patients occupy health states F0-F1 at baseline	Patients in these health states would be considered as having HDV disease burden that is too mild to initiate treatment with bulevirtide in clinical practice, according to guidelines.
Response rate increases beyond the observed trial period	Analysis of the IPD showed that response continued to increase between the key 24 and 48 week timepoints.
Patients who achieve combined response have a reduced risk of disease progression compared to suboptimal responders	The hazard ratios that inform disease progression for suboptimal (virologic) responders are based on data linking the

	impact of virological markers on disease progression. It is assumed that achievement of biochemical response, i.e., ALT normalisation (complete responders) in addition to virologic response indicates that the liver is not showing signs of inflammation and thus no disease progression would occur.

B.3.10 Base-case results

Base-case incremental cost-effectiveness analysis results

The cost-effectiveness analysis shows that bulevirtide is more effective than BSC (incremental gain of [redacted] QALYs) however it is also associated with higher incremental costs ([redacted]). The resulting incremental cost-effectiveness ratio (ICER) of £39,921 per QALY is slightly above the upper limit of the severity modifier threshold of £36,000 per QALY. A breakdown of the base-case incremental cost-effectiveness results are presented in Table 70. It should be noted that there is also a considerable gain in life years (5.96 years) with bulevirtide compared to BSC.

Table 70: Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
BSC	[redacted]	8.35	[redacted]	-	-	-	-	-
Bulevirtide	[redacted]	14.31	[redacted]	[redacted]	5.96	[redacted]	£39,921	£39,921

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 71: Net health benefit

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £24,000	NHB at £36,000
BSC	[redacted]	[redacted]	-			
Bulevirtide	[redacted]	[redacted]	[redacted]	[redacted]	-3.77	-0.62

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; NHB, net health benefi

B.3.11 Exploring uncertainty

Probabilistic sensitivity analysis

The PSA was performed to explore the uncertainty around key model parameters. The PSA was conducted by varying these parameters using their upper and lower bound values and a distribution was assigned to these parameters. These uncertainty estimates are provided in Appendix M. 1,500 simulations were sufficient to produce stable mean ICER estimates for the probabilistic sensitivity analysis (PSA). The probabilistic cost-effectiveness results are reported in Table 72. The incremental costs are slightly higher than those observed in the base-case ([redacted] vs. [redacted]), whilst the incremental QALYs are slightly higher ([redacted] vs. [redacted]), leading to a slightly higher ICER of £41,758 compared to the base-case ICER of £39,921.

Output from the PSA iterations is presented as scatter points on the cost-effectiveness plane in Figure 18. All points lie in the northeast quadrants of the plane, indicating that bulevirtide is more costly and more effective compared to BSC. The cost-effectiveness acceptability curve (CEAC) is presented in Figure 19. The CEAC shows that the probability of bulevirtide being cost-effective increases in line with the WTP threshold.

The probability that bulevirtide was the most cost-effective treatment at a willingness-to-pay (WTP) threshold of £36,000/QALY was 8%.

Table 72: Probabilistic cost-effectiveness results

Technologies	Total costs (£)	Total QALYs	Incremental. costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
BSC	[redacted]	[redacted]	-	-	-	-
Bulevirtide	[redacted]	[redacted]	[redacted]	[redacted]	£41,758	£41,758

Figure 18: PSA scatterplot

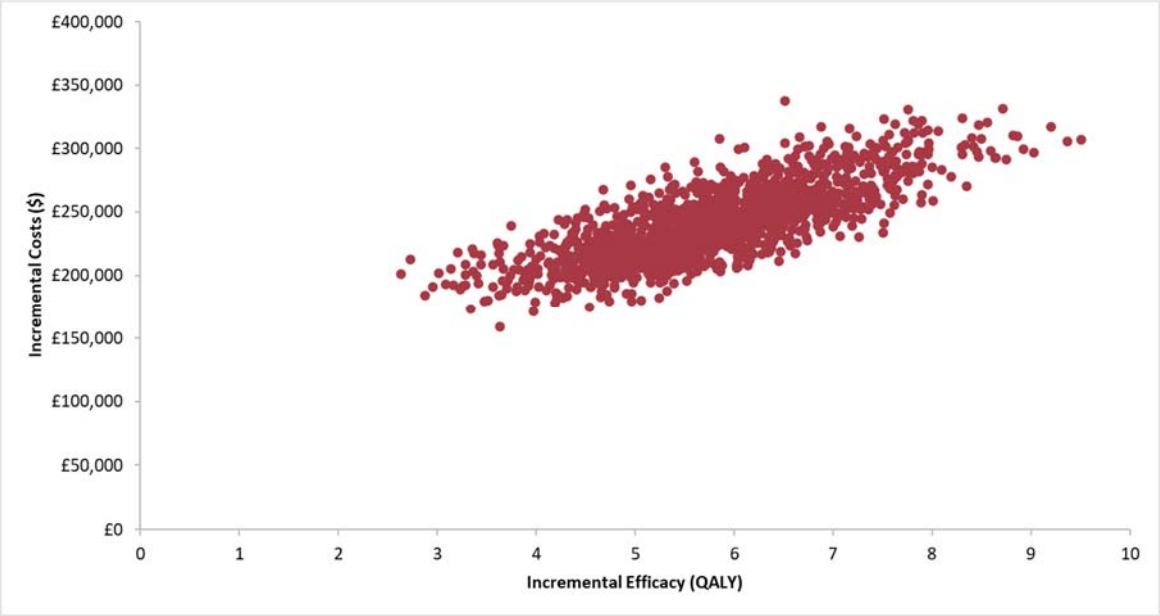
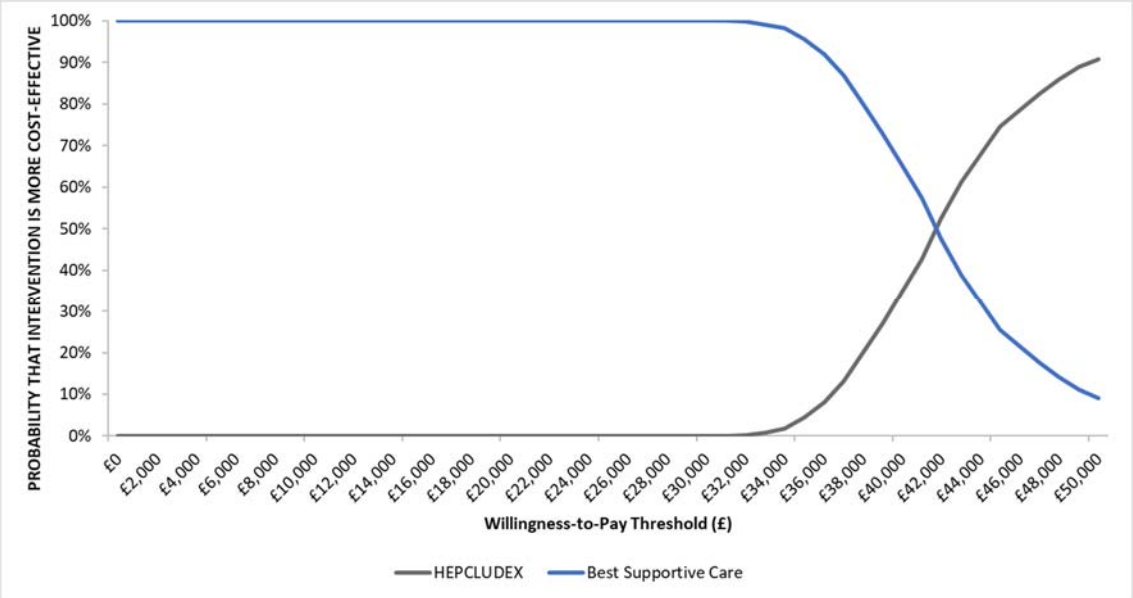


Figure 19: Cost-effectiveness acceptability curve, bulevirtide vs BSC



Deterministic sensitivity analysis

One-way deterministic sensitivity analyses (OWSA) were conducted to examine the sensitivity of the model result to lower and upper estimates for parameter values. Only parameters which could be varied independently were varied in OWSA. In

cases where no upper or lower estimate for a parameter value was available, parameters were varied by 20% of the mean. The upper and lower parameter estimates that were used in the OWSA are presented in Appendix M.

The OWSA results are presented in the tornado diagram (Figure 20) where each parameter (y axis) is ranked (highest to lowest) by its impact on the model result. Only the 20 parameters that had the largest impact on the results are included in the tornado diagrams.

The most influential parameter across all the comparisons was the adherence to bulevirtide (which alters the drug costs). Treatment adherence refers to the proportion of patients complying with daily treatment as prescribed. When varied between its upper and lower bounds, this parameter led to differences in the ICERs ranging from £27,602 to £41,443 per QALY. Other influential parameters include the proportion of composite responders at week 48 in the BSC arm, the utility gain for responders and the proportion of virologic responders at week 24 in the BSC arm.

Figure 20: OWSA results, bulevirtide vs BSC

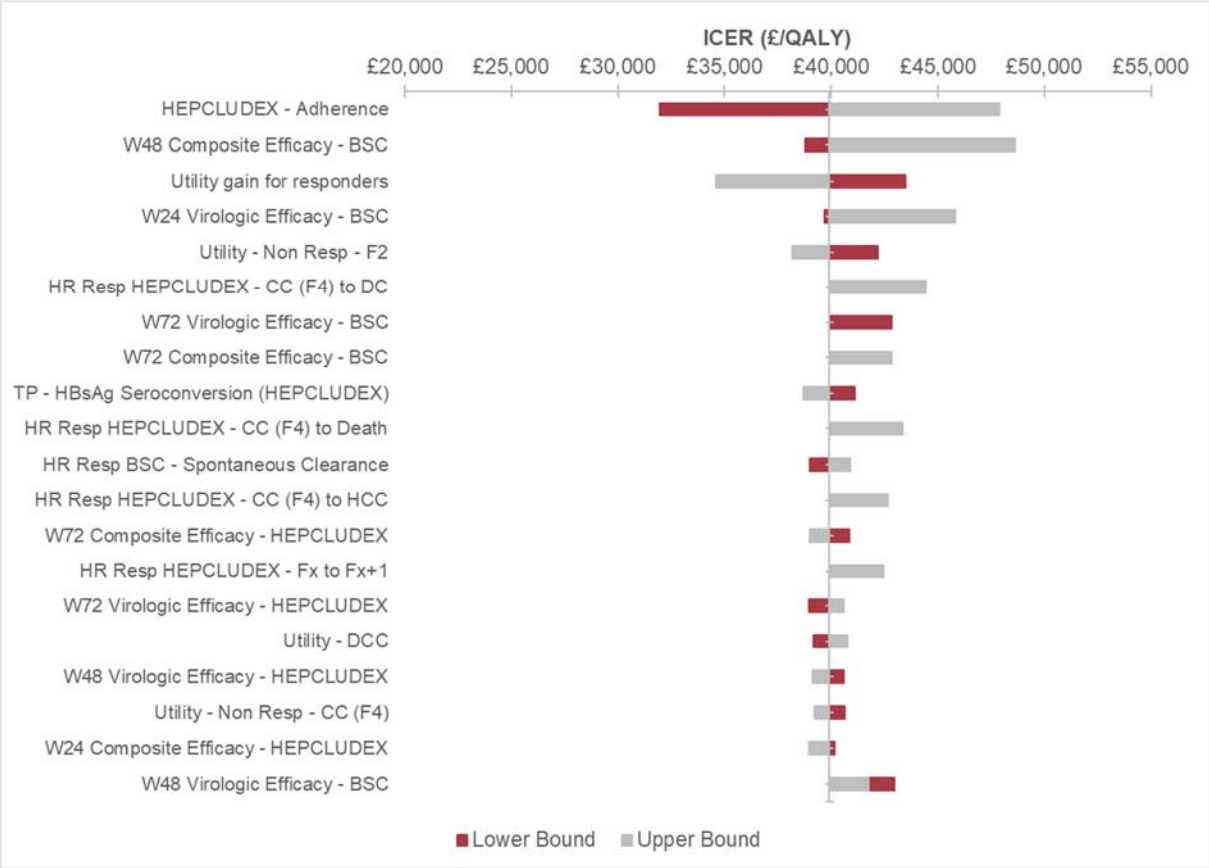


Table 73: OWSA results, bulevirtide vs BSC

Parameter	Lower bound ICER	Upper bound ICER	Difference
HEPCLUDEX - Adherence	£31,939	£47,904	£15,965
W48 Composite Efficacy - BSC	£38,773	£48,644	£9,871
Utility gain for responders	£43,501	£34,599	£8,902
W24 Virologic Efficacy - BSC	£39,696	£45,816	£6,119
Utility - Non Resp - F2	£42,194	£38,160	£4,034
HR Resp HEPCLUDEX - CC (F4) to DC	£41,433	£44,419	£2,985
W72 Virologic Efficacy - BSC	£42,854	£39,921	£2,933
W72 Composite Efficacy - BSC	£39,921	£42,854	£2,933
TP - HBsAg Seroconversion (HEPCLUDEX)	£41,112	£38,686	£2,426
HR Resp HEPCLUDEX - CC (F4) to Death	£41,033	£43,354	£2,321
HR Resp BSC - Spontaneous Clearance	£38,985	£40,881	£1,896
HR Resp HEPCLUDEX - CC (F4) to HCC	£40,822	£42,688	£1,866
W72 Composite Efficacy - HEPCLUDEX	£40,846	£38,985	£1,861
HR Resp HEPCLUDEX - Fx to Fx+1	£40,708	£42,436	£1,728
W72 Virologic Efficacy - HEPCLUDEX	£38,960	£40,602	£1,642
Utility - DCC	£39,150	£40,755	£1,604
W48 Virologic Efficacy - HEPCLUDEX	£40,609	£39,144	£1,465
Utility - Non Resp - CC (F4)	£40,648	£39,220	£1,429
W24 Composite Efficacy - HEPCLUDEX	£40,169	£38,964	£1,204
W48 Virologic Efficacy - BSC	£42,955	£41,752	£1,203

Scenario analysis

The sensitivity of the model results to changes in key assumptions or parameters underpinning the model base-case was examined through several scenario analyses. The scenario analyses results are presented in Table 74. The scenario that had the largest impact upon the cost-effectiveness results was selecting virologic response as the choice of responder definition, compared to combined virologic and biochemical (composite) response as in the base-case. In this scenario, whilst the incremental costs reduced from [redacted] to [redacted] the incremental QALYs also reduced from [redacted] to [redacted] QALYs (because progression is only assumed to be reduced instead of halted), leading to a higher ICER of £50,421 per QALY vs. the base case. None of the other scenarios explored reduced the incremental QALY gain below 4 QALYs.

Other scenarios that had the most significant impact upon the ICER were the removal of the utility gain for responders and changing the hazard ratios for progression in complete responders to be double that for partial responders (e.g.,

0.22 in a partial responder is assumed to be 0.11 in a complete responder). When the utility gain for responders was removed, this led to a reduction in incremental QALYs from [redacted] to [redacted]. The ICER for this scenario was £43,501 per QALY. In the scenario where the hazard ratios for progression in complete responders were set to double that for the partial responders, there was a decrease in both incremental costs, from [redacted] to [redacted] and QALYs, from [redacted] to [redacted], leading to an ICER of [redacted] per QALY.

Table 74: Scenario analyses results

Structural assumption	Base-case scenario	Other scenarios considered	Incremental costs	Incremental QALYs	ICER vs. BSC
Base-case			[redacted]	[redacted]	[redacted]
Patients' baseline fibrosis status	F2-F4	F3-F4	[redacted]	[redacted]	[redacted]
Inclusion of utility gain for responders	Included	Excluded	[redacted]	[redacted]	[redacted]
Fibrosis regression	Included	Excluded	[redacted]	[redacted]	[redacted]
Hazard ratios for progression in complete responders	Value of 0.001	Hazard ratios are half of that of the partial responders	[redacted]	[redacted]	[redacted]
Definition of responder	Composite	Virologic	[redacted]	[redacted]	[redacted]
Extrapolation of 48-week MYR 301 response data	Yes	No	[redacted]	[redacted]	[redacted]
Source of non-responder health state utility values for mild-moderate health states	CHB meta-analysis for F0-F4	MYR 301 for F0-F4	[redacted]	[redacted]	[redacted]
Source of health state utility values for all non-responder health states	CHB meta-analysis	Chronic HCV meta-analysis	[redacted]	[redacted]	[redacted]

B.3.12 Subgroup analysis

No subgroup analyses were conducted as part of this economic evaluation.

B.3.13 Benefits not captured in the QALY calculation

The model currently assumes that only complete responders have a utility gain from bulevirtide. However, a large proportion of patients achieved ALT levels 1-2x within ULN and these patients are also likely to derive a utility gain from treatment. The utility gains in the model can therefore be considered to be underestimated.

Additionally, chronic sickness can have a detrimental impact on other family members' quality of life (spill-over effect) including that of young children.

B.3.14 Validation

Validation of cost-effectiveness analysis

The model has undergone thorough internal validation. The model was developed internally by a team of health economists. The structure and clinical assumptions of the model were discussed and ratified as part of an advisory board which included UK clinical and health economic experts. All feedback and external ratification went into the final model and this written submission.

B.3.15 Interpretation and conclusions of economic evidence

Bulevirtide meets the criteria for a severity weighting of 1.2 and is cost-effective at the WTP threshold of £36,000 per QALY. While bulevirtide is associated with additional costs, it is also associated with substantial discounted life years and QALYs gains. Unusually for an orphan condition, results were relatively robust to changes in structural and parameter assumptions, however longer-term data from MYR301 is expected to help reduce some of the uncertainty around the estimates of cost-effectiveness.

Strengths of the economic analysis

- The analysis considered the key patient group likely to be offered bulevirtide in the UK NHS. That is, adults with CHD who have compensated liver disease and evidence of significant fibrosis (METAVIR stage greater than or equal to F2) whose disease has responded inadequately to interferon-based therapy, or who are ineligible to receive interferon-based therapy due to intolerance or contraindication.

- The economic analysis uses IPD from the pivotal MYR 301 study which represents the best available clinical and safety data for bulevirtide to date. Furthermore, the data informing the clinical efficacy parameters have been obtained from a sub-group of patients who were interferon-based therapy experienced and thus align closely with the population of interest.

- The model used a well-recognised framework for evaluation of hepatitis treatments. While this is the first evaluation in hepatitis delta, differences such as rate of progression and disease monitoring have been incorporated into the model.

- The model was informed by a well-designed randomised clinical trial and a comprehensive review of the HDV literature for extrapolation of surrogate to final outcomes.

- Identification of natural history inputs, costs and utilities were obtained by systematic review and meta-analysis of the relevant literature.

Limitations of the economic analysis

- As an orphan disease, paucity of data means that a number of assumptions have had to be made regarding disease progression rates and the impact of bulevirtide on these, which leads to some additional uncertainty.

- Potential quality of life gains in patients who saw improvements in their ALT levels but failed to achieve the primary endpoint have not been captured. Nor has the impact of quality of life of other family members.
- The clinical data informing the model is based on interim 48-week data rather than the full 240-week data which therefore increases the uncertainty around the cost-effectiveness estimates. However, more long-term data will become available which may help resolve some of this uncertainty; in turn providing greater confidence in the estimate of cost-effectiveness.

B.4 References

1. Ni Y, Lempp FA, Mehrle S, Nkongolo S, Kaufman C, Fälth M, et al. Hepatitis B and D viruses exploit sodium taurocholate co-transporting polypeptide for species-specific entry into hepatocytes. Gastroenterology [Internet]. 2014 [cited 2022 Mar 14];146(4). Available from: https://pubmed.ncbi.nlm.nih.gov/24361467/

2. Yan H, Zhong G, Xu G, He W, Jing Z, Gao Z, et al. Sodium taurocholate cotransporting polypeptide is a functional receptor for human hepatitis B and D virus. Elife [Internet]. 2012 Nov 13 [cited 2022 Mar 14];1(1). Available from: /pmc/articles/PMC3485615/

3. European Medicines Agency. Hepcludex: EPAR - Public assessment report [Internet]. 2020 [cited 2022 Feb 20]. Available from: https://www.ema.europa.eu/en/documents/assessment-report/hepcludex-epar-public-assessment-report_en.pdf

4. Farci P, Niro GA. Current and future management of chronic hepatitis D. Gastroenterol Hepatol [Internet]. 2018 Jun 1 [cited 2021 Oct 26];14(6):342–51. Available from: /pmc/articles/PMC6111511/

5. AMNOG Dossier Module 1 HEPCLUDEX (bulevirtide). Summary of the statements in the dossier. 2020.

6. MYR Pharmaceuticals. Mechanism of action - Bulevirtide.

7. European Medicines Agency. Hepcludex [Internet]. 2021 [cited 2021 Oct 26]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/hepcludex

8. Medicines and Healthcare Products Regulatory Agency (MHRA). Hepcludex - Summary of Product Characteristics (SmPC) [Internet]. 2021 [cited 2022 Mar 25]. Available from: https://mhraproducts4853.blob.core.windows.net/docs/ccbbd004d098f9661d5ba8c7bb961d80545bec1e

9. Koh C, Da BL, Glenn JS. HBV/HDV Coinfection: A Challenge for Therapeutics [Internet]. Vol. 23, Clinics in Liver Disease. NIH Public Access; 2019 [cited 2021 Oct 26]. p. 557–72. Available from: /pmc/articles/PMC6659751/

10. Miao Z, Zhang S, Ou X, Li S, Ma Z, Wang W, et al. Estimating the global prevalence, disease progression, and clinical outcome of hepatitis delta virus infection. J Infect Dis [Internet]. 2020 May 15 [cited 2021 Oct 26];221(10):1677–87. Available from: /pmc/articles/PMC7184909/

11. Buti M, Homs M, Rodriguez-Frias F, Funalleras G, Jardí R, Sauleda S, et al. Clinical outcome of acute and chronic hepatitis delta over time: a long-term follow-up study. J Viral Hepat [Internet]. 2011 Jun [cited 2022 Mar 15];18(6):434–42. Available from: https://pubmed.ncbi.nlm.nih.gov/20546496/

12. Yurdaydin C, Idilman R, Bozkaya H, Bozdayi AM. Natural history and treatment of chronic delta hepatitis. J Viral Hepat [Internet]. 2010 [cited 2022 Mar 15];17(11):749–56. Available from: https://pubmed.ncbi.nlm.nih.gov/20723036/

13. Negro F. Hepatitis D virus coinfection and superinfection. Cold Spring Harb Perspect Med [Internet]. 2014 [cited 2021 Oct 26];4(11). Available from: /pmc/articles/PMC4208707/

14. Healthline. Hepatitis D [Internet]. [cited 2021 Oct 26]. Available from: https://www.healthline.com/health/delta-agent-hepatitis-d

15. Huang YH, Wu JC, Sheng WY, Huo TI, Chang FY, Lee SD. Diagnostic value of anti-hepatitis D virus (HDV) antibodies revisited: A study of total and IgM anti-HDV compared with detection of HDV-RNA by polymerase chain reaction. J Gastroenterol Hepatol [Internet]. 1998 Jan 1 [cited 2021 Oct 26];13(1):57–61. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/j.1440-1746.1998.tb00546.x

16. Heidrich B, Yurdaydin C, Kabaçam G, Ratsch BA, Zachou K, Bremer B, et al. Late HDV RNA relapse after peginterferon alpha-based therapy of chronic

hepatitis delta. Hepatology [Internet]. 2014 Jul 1 [cited 2022 Feb 17];60(1):87–97. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/hep.27102

17. Béguelin C, Moradpour D, Sahli R, Suter-Riniker F, Lüthi A, Cavassini M, et al. Hepatitis delta-associated mortality in HIV/HBV-coinfected patients. J Hepatol [Internet]. 2017 Feb 1 [cited 2022 Mar 15];66(2):297–303. Available from: https://pubmed.ncbi.nlm.nih.gov/27746337/

18. Noureddin M, Gish R. Hepatitis delta: Epidemiology, diagnosis and management 36 years after discovery. Curr Gastroenterol Rep [Internet]. 2014 [cited 2021 Oct 26];16(1). Available from: /pmc/articles/PMC3918112/

19. Fattovich G, Giustina G, Christensen E, Pantalena M, Zagni I, Realdi G, et al. Influence of hepatitis delta virus infection on morbidity and mortality in compensated cirrhosis type B. Gut [Internet]. 2000 [cited 2021 Oct 26];46(3):420–6. Available from: /pmc/articles/PMC1727859/

20. Da BL, Heller T, Koh C. Hepatitis D infection: From initial discovery to current investigational therapies [Internet]. Vol. 7, Gastroenterology Report. Oxford University Press; 2019 [cited 2021 Oct 26]. p. 231–45. Available from: /pmc/articles/PMC6691517/

21. Grabowski J, Wedemeyer H. Hepatitis delta: Immunopathogenesis and clinical challenges [Internet]. Vol. 28, Digestive Diseases. Karger Publishers; 2010 [cited 2021 Oct 26]. p. 133–8. Available from: https://www.karger.com/Article/FullText/282076

22. Bockmann JH, Grube M, Hamed V, Von Felden J, Landahl J, Wehmeyer M, et al. High rates of cirrhosis and severe clinical events in patients with HBV/HDV co-infection: longitudinal analysis of a German cohort. BMC Gastroenterol [Internet]. 2020 Jan 30 [cited 2021 Oct 26];20(1). Available from: /pmc/articles/PMC6993357/

23. Axley P, Mudumbi S, Sarker S, Kuo YF, Singal A. Patients with stage 3 compared to stage 4 liver fibrosis have lower frequency of and longer time to

liver disease complications. PLoS One [Internet]. 2018 May 1 [cited 2021 Oct 26];13(5). Available from: /pmc/articles/PMC5944985/

24. Golabi P, Fazel S, Otgonsuren M, Sayiner M, Locklear CT, Younossi ZM. Mortality assessment of patients with hepatocellular carcinoma according to underlying disease and treatment modalities. Med (United States) [Internet]. 2017 Mar 1 [cited 2021 Oct 26];96(9). Available from: /pmc/articles/PMC5340426/

25. Cornberg M, Lok ASF, Terrault NA, Zoulim F, Berg T, Brunetto MR, et al. Guidance for Design and Endpoints of Clinical Trials in Chronic Hepatitis B—Report From the 2019 EASL-AASLD HBV Treatment Endpoints Conference. Hepatology [Internet]. 2020 Mar 1 [cited 2022 Feb 10];71(3):1070–92. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/hep.31030

26. European Medicines Agency. Hepcludex: Orphan Maintenance Assessment Report [Internet]. 2020 [cited 2021 Nov 18]. Available from: https://www.ema.europa.eu/en/documents/orphan-maintenance-report/hepcludex-orphan-maintenance-assessment-report_en.pdf

27. Lampertico P, Agarwal K, Berg T, Buti M, Janssen HLA, Papatheodoridis G, et al. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol [Internet]. 2017 Aug 1 [cited 2021 Oct 26];67(2):370–98. Available from: https://pubmed.ncbi.nlm.nih.gov/28427875/

28. Rizzetto M, Hamid S, Negro F. The changing context of hepatitis D. J Hepatol [Internet]. 2021 May 1 [cited 2022 Jan 31];74(5):1200–11. Available from: https://pubmed.ncbi.nlm.nih.gov/33484770/

29. Sleijfer S, Bannink M, Van Gool AR, Kruit WHJ, Stoter G. Side effects of interferon-alpha therapy. Pharm World Sci [Internet]. 2005 Dec [cited 2022 Jan 31];27(6):423–31. Available from: https://pubmed.ncbi.nlm.nih.gov/16341948/

30. Gilman C, Heller T, Koh C. Chronic hepatitis delta: A state-of-the-art review and new therapies [Internet]. Vol. 25, World Journal of Gastroenterology.

Baishideng Publishing Group Inc; 2019 [cited 2021 Oct 26]. p. 4580–97. Available from: /pmc/articles/PMC6718034/

31. GSI - Data on file. Advisory Board Report. 2022.

32. British Liver Trust. Hepatitis B [Internet]. 2022 [cited 2021 Jan 26]. Available from: https://britishlivertrust.org.uk/information-and-support/living-with-a-liver-condition/liver-conditions/hepatitis-b/

33. Stockdale AJ, Kreuels B, Henrion MYR, Giorgi E, Kyomuhangi I, de Martel C, et al. The global prevalence of hepatitis D virus infection: Systematic review and meta-analysis. J Hepatol [Internet]. 2020 Sep 1 [cited 2021 Oct 26];73(3):523–32. Available from: https://pubmed.ncbi.nlm.nih.gov/32335166/

34. GSI - Data on file. Gilead Internal Assumption. 2022.

35. Romeo R, Del Ninno E, Rumi M, Russo A, Sangiovanni A, de Franchis R, et al. A 28-Year Study of the Course of Hepatitis Δ Infection: A Risk Factor for Cirrhosis and Hepatocellular Carcinoma. Gastroenterology [Internet]. 2009 [cited 2021 Oct 26];136(5):1629–38. Available from: https://pubmed.ncbi.nlm.nih.gov/19208358/

36. Roulot D, Brichler S, Layese R, BenAbdesselam Z, Zoulim F, Thibault V, et al. Origin, HDV genotype and persistent viremia determine outcome and treatment response in patients with chronic hepatitis delta. J Hepatol [Internet]. 2020 Nov 1 [cited 2021 Oct 26];73(5):1046–62. Available from: https://pubmed.ncbi.nlm.nih.gov/32634548/

37. Abbas Z, Abbas M, Abbas S, Shazi L. Hepatitis D and hepatocellular carcinoma. World J Hepatol [Internet]. 2015 [cited 2021 Oct 26];7(5):777–86. Available from: /pmc/articles/PMC4404383/

38. Kamal H, Westman G, Falconer K, Duberg AS, Weiland O, Haverinen S, et al. Long-Term Study of Hepatitis Delta Virus Infection at Secondary Care Centers: The Impact of Viremia on Liver-Related Outcomes. Hepatology [Internet]. 2020 Oct 1 [cited 2022 Feb 16];72(4):1177–90. Available from:

https://pubmed.ncbi.nlm.nih.gov/32145073/

39. Westbrook RH, Dusheiko G. Natural history of hepatitis C [Internet]. Vol. 61, Journal of Hepatology. J Hepatol; 2014 [cited 2021 Oct 26]. p. S58–68. Available from: https://pubmed.ncbi.nlm.nih.gov/25443346/

40. Fattovich G. Natural history and prognosis of hepatitis B [Internet]. Vol. 23, Seminars in Liver Disease. Copyright © 2002 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA. Tel.: +1(212) 584-4662; 2003 [cited 2021 Oct 26]. p. 47–58. Available from: http://www.thieme-connect.com/products/ejournals/html/10.1055/s-2003-37590

41. Grebely J, Talwalkar JA. Recognizing and preventing death from compensated cirrhosis in the community [Internet]. Vol. 32, Liver International. NIH Public Access; 2012 [cited 2021 Oct 28]. p. 2–4. Available from: /pmc/articles/PMC3237719/

42. Bataller R, Brenner DA. Liver fibrosis [Internet]. Vol. 115, Journal of Clinical Investigation. American Society for Clinical Investigation; 2005 [cited 2021 Oct 26]. p. 209–18. Available from: /pmc/articles/PMC546435/

43. Muhammad H, Tehreem A, Hammami MB, Ting PS, Gurakar A, Idilman R. Hepatitis D virus and liver transplantation: Indications and outcomes. World J Hepatol [Internet]. 2021 [cited 2021 Oct 26];13(3):291–9. Available from: /pmc/articles/PMC8006082/

44. 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 [Internet]. 2020 Sep 1 [cited 2021 Oct 26];73(3):533–9. Available from: https://pubmed.ncbi.nlm.nih.gov/32151618/

45. Nault JC. Pathogenesis of hepatocellular carcinoma according to aetiology [Internet]. Vol. 28, Best Practice and Research: Clinical Gastroenterology. Best Pract Res Clin Gastroenterol; 2014 [cited 2021 Oct 26]. p. 937–47. Available from: https://pubmed.ncbi.nlm.nih.gov/25260319/

46. Cancer Research UK. Cancer mortality for common cancers | Cancer Research UK [Internet]. 2021 [cited 2022 Mar 14]. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/mortality/common-cancers-compared#heading-Zero

47. Burton A, Tataru D, Driver RJ, Bird TG, Huws D, Wallace D, et al. Primary liver cancer in the UK: Incidence, incidence-based mortality, and survival by subtype, sex, and nation. JHEP Reports [Internet]. 2021 Apr 1 [cited 2021 Oct 26];3(2). Available from: https://pubmed.ncbi.nlm.nih.gov/33748727/

48. Ransford R, Gunson B, Mayer D, Neuberger J, Christensen E. Effect on outcome of the lengthening waiting list for liver transplantation [Internet]. Vol. 47, Gut. BMJ Publishing Group; 2000 [cited 2021 Oct 26]. p. 441–3. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1728057/

49. Kim WR, Therneau TM, Benson JT, Kremers WK, Rosen CB, Gores GJ, et al. Deaths on the liver transplant waiting list: An analysis of competing risks. Hepatology [Internet]. 2006 Feb [cited 2021 Oct 26];43(2):345–51. Available from: https://pubmed.ncbi.nlm.nih.gov/16440361/

50. Ferrarese A, Sciarrone S, Gambato M, Germani G, Senzolo M, Boccagni P, et al. Letter: clinical outcomes of patients with hepatitis D infection in the liver transplant setting [Internet]. Vol. 51, Alimentary Pharmacology and Therapeutics. Aliment Pharmacol Ther; 2020 [cited 2021 Oct 26]. p. 482–3. Available from: https://pubmed.ncbi.nlm.nih.gov/31990393/

51. Mayo Clinic. Liver transplant [Internet]. [cited 2021 Oct 26]. Available from: https://www.mayoclinic.org/tests-procedures/liver-transplant/about/pac-20384842

52. Feld JJ, Wong DKH, Heathcote EJ. Endpoints of therapy in chronic hepatitis B. Hepatology [Internet]. 2009 May [cited 2022 Feb 24];49(5 Suppl). Available from: https://pubmed.ncbi.nlm.nih.gov/19399800/

53. Food and Drug Administration (FDA). Chronic Hepatitis D Virus Infection:

Developing Drugs for Treatment Guidance for Industry DRAFT GUIDANCE. 2019 [cited 2022 Mar 15]; Available from: https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

54. Braga WSM, De Oliveira CMC, De Araújo JR, Castilho MDC, Rocha JM, Gimaque JBDL, et al. Chronic HDV/HBV co-infection: predictors of disease stage---a case series of HDV-3 patients. J Hepatol [Internet]. 2014 Dec 1 [cited 2022 Mar 15];61(6):1205–11. Available from: https://pubmed.ncbi.nlm.nih.gov/24905491/

55. Yamashiro T, Nagayama K, Enomoto N, Watanabe H, Miyagi T, Nakasone H, et al. Quantitation of the level of hepatitis delta virus RNA in serum, by real-time polymerase chain reaction--and its possible correlation with the clinical stage of liver disease. J Infect Dis [Internet]. 2004 Apr 1 [cited 2022 Feb 16];189(7):1151–7. Available from: https://pubmed.ncbi.nlm.nih.gov/15031781/

56. GSI - Data on file. Hepatitis Delta Virus Infection in Patients with Chronic Hepatitis B is Associated with Greater Risk of Liver Disease Progression and Liver-Related Mortality: A Systematic Review and Meta-Analysis. 2022.

57. AMNOG Dossier Module 4A HEPCLUDEX (bulevirtide). Medical benefits and medical added value, patient groups with therapeutically significant added value. 2020.

58. GSI - Data on file. MYR 202 Clinical Study Report. 2019;

59. GSI - Data on file. MYR 301 Clinical Study Report. 2022;

60. Chotiyaputta W, Lok ASF. Endpoints of hepatitis B treatment. J Viral Hepat [Internet]. 2010 Oct [cited 2022 Feb 16];17(10):675–84. Available from: https://pubmed.ncbi.nlm.nih.gov/20840331/

61. Chen CJ, Yang HI. Natural history of chronic hepatitis B REVEALed. J Gastroenterol Hepatol [Internet]. 2011 [cited 2022 Mar 30];26(4):628–38. Available from: https://pubmed.ncbi.nlm.nih.gov/21323729/

62. Zachou K, Yurdaydin C, Drebber U, Dalekos GN, Erhardt A, Cakaloglu Y, et al. Quantitative HBsAg and HDV-RNA levels in chronic delta hepatitis. Liver Int [Internet]. 2010 Mar [cited 2022 Mar 30];30(3):430–7. Available from: https://pubmed.ncbi.nlm.nih.gov/19840253/

63. Kim WR, Flamm SL, Di Bisceglie AM, Bodenheimer HC. Serum activity of alanine aminotransferase (ALT) as an indicator of health and disease. Hepatology [Internet]. 2008 Apr 1 [cited 2022 Feb 17];47(4):1363–70. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/hep.22109

64. Choi J, Kim GA, Han S, Lim YS. Earlier Alanine Aminotransferase Normalization During Antiviral Treatment Is Independently Associated With Lower Risk of Hepatocellular Carcinoma in Chronic Hepatitis B. Am J Gastroenterol [Internet]. 2020 Mar 1 [cited 2022 Mar 15];115(3):406–14. Available from: https://pubmed.ncbi.nlm.nih.gov/31895708/

65. Wong GLH, Chan HLY, Tse YK, Yip TCF, Lam KLY, Lui GCY, et al. Normal on-treatment ALT during antiviral treatment is associated with a lower risk of hepatic events in patients with chronic hepatitis B. J Hepatol [Internet]. 2018 Oct 1 [cited 2022 Mar 30];69(4):793–802. Available from: https://pubmed.ncbi.nlm.nih.gov/29758335/

66. Buti M, Stepanova M, Palom A, Riveiro-Barciela M, Nader F, Roade L, et al. Chronic hepatitis D associated with worse patient-reported outcomes than chronic hepatitis B. JHEP Reports [Internet]. 2021 Jun 1 [cited 2021 Oct 26];3(3). Available from: /pmc/articles/PMC8141931/

67. Stahmeyer JT, Becker H, Orlemann AL, Krauth C, Manns MP, Wedemeyer H. HBV-Infektionen in Deutschland - Versorgungskosten in einem Real-life-Setting. Z Gastroenterol [Internet]. 2017 Nov 1 [cited 2021 Oct 26];55(11):1103–12. Available from: https://pubmed.ncbi.nlm.nih.gov/29141265/

68. Dagli O, Mutlu EA. Depression scores of delta hepatitis patients treated with pegylated interferon alfa. Int J Clin Exp Med [Internet]. 2018 [cited 2021 Oct

26];11(12):13827–31. Available from: www.ijcem.com/

69. Elsaid MI, Li Y, John T, Narayanan N, Catalano C, Rustgi VK. Economic and Health Care Burdens of Hepatitis Delta: A Study of Commercially Insured Adults in the United States. Hepatology [Internet]. 2020 Aug 1 [cited 2021 Oct 26];72(2):399–411. Available from: https://pubmed.ncbi.nlm.nih.gov/31804707/

70. Goyal A, Murray JM. Cost-Effectiveness of Peg-Interferon, Interferon and Oral Nucleoside Analogues in the Treatment of Chronic Hepatitis B and D Infections in China. Clin Drug Investig [Internet]. 2016 Aug 1 [cited 2021 Oct 26];36(8):637–48. Available from: https://pubmed.ncbi.nlm.nih.gov/27166628/

71. Shah PA, Choudhry S, Reyes KJC, Lau DTY. An update on the management of chronic hepatitis D [Internet]. Vol. 7, Gastroenterology Report. Oxford Academic; 2019 [cited 2021 Oct 28]. p. 396–402. Available from: https://academic.oup.com/gastro/article/7/6/396/5601119

72. National Institute for Health and Care Excellence. Hepatitis B (chronic): diagnosis and management | Guidance | NICE [Internet]. 2017 [cited 2021 Oct 26]. Available from: https://www.nice.org.uk/guidance/cg165/ifp/chapter/drug-treatment

73. European Medicines Agency. Pegasys - Summary of Product Characteristics (SmPC) [Internet]. 2022. Available from: https://www.ema.europa.eu/en/documents/product-information/pegasys-epar-product-information_en.pdf

74. National Institute for Health and Care Excellence. Adefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B | Guidance | NICE [Internet]. 2006 [cited 2021 Oct 26]. Available from: https://www.nice.org.uk/guidance/TA96

75. Bremer B, Anastasiou OE, Hardtke S, Caruntu FA, Curescu MG, Yalcin K, et al. Residual low HDV viraemia is associated HDV RNA relapse after PEG-IFNa-based antiviral treatment of hepatitis delta: Results from the HIDIT-II

study. Liver Int [Internet]. 2021 Feb 1 [cited 2022 Jan 31];41(2):295–9. Available from: https://pubmed.ncbi.nlm.nih.gov/33217778/

76. Wedemeyer H, Yurdaydin C, Hardtke S, Caruntu FA, Curescu MG, Yalcin K, et al. Peginterferon alfa-2a plus tenofovir disoproxil fumarate for hepatitis D (HIDIT-II): a randomised, placebo controlled, phase 2 trial. Lancet Infect Dis [Internet]. 2019 Mar 1 [cited 2022 Feb 21];19(3):275–86. Available from: http://www.thelancet.com/article/S1473309918306637/fulltext

77. Cross TJS, Rizzi P, Horner M, Jolly A, Hussain MJ, Smith HM, et al. The increasing prevalence of hepatitis delta virus (HDV) infection in South London. J Med Virol [Internet]. 2008 Feb [cited 2021 Nov 16];80(2):277–82. Available from: https://pubmed.ncbi.nlm.nih.gov/18098143/

78. Spaan M, Carey I, Bruce M, Shang D, Horner M, Dusheiko G, et al. Hepatitis delta genotype 5 is associated with favourable disease outcome and better response to treatment compared to genotype 1. J Hepatol [Internet]. 2020;72(6):1097–104. Available from: http://dx.doi.org/10.1016/j.jhep.2019.12.028

79. Wedemeyer H, Aleman S, Andreone P, Blank A, Brunetto M, Bogomolov P, et al. Bulevirtide Monotherapy at Low and High Doses in Patients With Chronic Hepatitis Delta: 24-Week Interim Data of the Phase 3 MYR301 Study. J Hepatol. 2021;75(2):S294-803.

80. Allweiss L, Volmari A, Ladiges Y, Eggers C, Giersch K, Schoeneweis K, et al. 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) [Internet]. 2021 [cited 2022 Mar 14]. Available from: https://natap.org/2021/AASLD/AASLD_56.htm

81. Wedemeyer H, Aleman S, Chulanov V, Hilgard G, Antonova J, Kaushik AM, et al. Treatment with bulevirtide improves patient reported outcomes in patients with chronic hepatitis delta (CHD): an interim exploratory analysis at week 24

[Internet]. 2020 [cited 2022 Feb 25]. Available from: https://www.natap.org/2021/AASLD/AASLD_17.htm

82. Wedemeyer H, Bogomolov P, Blank A, Allweiss L, Dandri-Petersen M, Bremer B, et al. 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. J Hepatol [Internet]. 2018 Apr [cited 2021 Nov 15];68:S3. Available from: https://www.researchgate.net/publication/324698205_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_HBVHDV_co-infection

83. Allweiss L, Dettmer C, Volz T, Giersch K, Alexandrov A, Wedemeyer H, et al. Strong intrahepatic decline of hepatitis D virus RNA and antigen after 24 weeks 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 [Internet]. 2018 [cited 2022 Feb 25]. Available from: https://www.natap.org/2018/EASL/EASL_90.htm

84. Allweiss L, Volz T, Wedemeyer H, Schöneweis K, Alexandrov A, Bockmann J, et al. 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. 35 Jahrestagung der Dtsch Arbeitsgemeinschaft zum Stud der Leber. 2019 Jan;57.

85. Wedemeyer H, Bogomolov P, Blank A, Bremer B, Voronkova N, Schoeneweis K, et al. Interim results of a multicenter, open-label phase 2b clinical trial to assess the safety and efficacy of Mycrludex B in combination with tenofovir in patients with HBV/HDV coinfection [Internet]. [cited 2022 Feb 25]. Available from: https://www.researchgate.net/publication/321017129_Interim_results_of_a_multicenter_open-

label_phase_2b_clinical_trial_to_assess_the_safety_and_efficacy_of_Mycrludex_B_in_combination_with_tenofovir_in_patients_with_HBVHDV_coinfection

86. Bogomolov P, Alexandrov A, Voronkova N, Macievich M, Kokina K, Petrachenkova M, et al. Treatment of chronic hepatitis D with the entry inhibitor myrcludex B: First results of a phase Ib/IIa study. J Hepatol [Internet]. 2016 Sep 1 [cited 2022 Feb 25];65(3):490–8. Available from: https://pubmed.ncbi.nlm.nih.gov/27132170/

87. Urban S, Bogomolov P, Voronkova N, Allweiss L, Dandri M, Schwab M, et al. A proof-of-concept Phase 2a clinical trial with HBV/HDV entry inhibitor Myrcludex B. Hepatology [Internet]. 2014 [cited 2022 Feb 25];60. Available from: https://www.researchgate.net/publication/280131392_A_proof-of-concept_Phase_2a_clinical_trial_with_HBVHDV_entry_inhibitor_Myrcludex_B

88. Wedemeyer H, Schöneweis K, Bogomolov PO, Voronkova N, Chulanov V, Stepanova T, et al. Final results of a multicenter, open-label phase 2 clinical trial (MYR203) to assess safety and efficacy of myrcludex B in with PEG-interferon Alpha 2a in patients with chronic HBV/HDV co-infection. Vol. 70, Journal of Hepatology. Elsevier BV; 2019 Apr.

89. Wedemeyer H, Bogomolov P, Blank A, Allweiss L, Dandri-Petersen M, Bremer B, et al. Final results of a multicenter, open-label phase 2b clinical trial to assess safety and efficacy of MyrcludexB in combination with Tenofovirin patients with HBV/HDV coinfection [Internet]. 2018 [cited 2022 Feb 25]. Available from: https://livertree.easl.eu/easl/2018/international.liver.congress/210647/heiner.wedemeyer.final.results.of.a.multicenter.open-label.phase.2b.clinical.html

90. Wedemeyer H, Schöneweis K, Bogomolov PO, Chulanov V, Stepanova T, Viacheslav M, et al. 48 weeks of high dose (10 mg) bulevirtide as monotherapy or with peginterferon alfa-2a in patients with chronic HBV/HDV co-infection. J Hepatol. 2020 Aug;73:S52–3.

91. Wedemeyer H, Schoeneweis K, Voronkova N, Chulanov V, Stepanova T,

Allweiss L, et al. Safety and Efficacy of 10mg (high-dose) bulevirtide (Myrcludex B) in combination with PEG-IFNa or TDF in patients with chronic HBV/HDV co-infection: interim results. [Internet]. 2019 [cited 2022 Feb 25]. Available from: https://www.natap.org/2019/AASLD/AASLD_68.htm

92. Wedemeyer H, Schöneweis K, Bogomolov P, Vorokova N, Chulanov V, Stepanova T, et al. Safety and Efficacy of 10 mg Myrcludex B/IFNa Combination Therapy in Patients with Chronic HBV/HDV Co-Infection. Z Gastroenterol [Internet]. 2020 Jan 3 [cited 2022 Feb 25];58(01):2.1. Available from: http://www.thieme-connect.de/products/ejournals/html/10.1055/s-0039-3402105

93. Asselah T, Arama SS, Bogomolov P, Bourliere M, Fontaine H, Gherlan GS, et al. 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 [Internet]. [cited 2022 Feb 25]. Available from: https://www.natap.org/2021/EASL/EASL_54.htm

94. European Association for the Study of the Liver. List of accepted abstracts [Internet]. 2022. Available from: https://easl.eu/wp-content/uploads/2022/04/ILC-2022-accepted-abstract-06.04.pdf

95. European Medicines Agency. Hepcludex - Summary of Product Characteristics (SmPC) [Internet]. 2020 [cited 2021 Oct 26]. Available from: https://www.ema.europa.eu/en/documents/product-information/hepcludex-epar-product-information_en.pdf

96. Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology [Internet]. 2018 Apr 1 [cited 2021 Oct 26];67(4):1560–99. Available from: https://pubmed.ncbi.nlm.nih.gov/29405329/

97. European Medicines Agency. Viread - Summary of Product Characteristics (SmPC) [Internet]. 2019. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/viread#product-

information-section

98. Centre for Reviews and Dissemination. Systematic Reviews: CRD"s guidance for undertaking reviews in health care [Internet]. 2009 [cited 2022 Feb 25]. Available from: www.york.ac.uk/inst/crd

99. GSI - Data on file. PEG-IFN Subgroup Analysis. 2022.

100. GSI - Data on file. ALT Visualisation Graphs Week 48. 2022.

101. Castera L, Yuen Chan HL, Arrese M, Afdhal N, Bedossa P, Friedrich-Rust M, et al. EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis. J Hepatol [Internet]. 2015 Jul 1 [cited 2022 Mar 14];63(1):237–64. Available from: https://pubmed.ncbi.nlm.nih.gov/25911335/

102. Marcellin P, Gane E, Buti M, Afdhal N, Sievert W, Jacobson IM, et al. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study. Lancet (London, England). 2013 Feb;381(9865):468–75.

103. Farci P, Roskams T, Chessa L, Peddis G, Mazzoleni AP, Scioscia R, et al. Long-term benefit of interferon α therapy of chronic hepatitis D: regression of advanced hepatic fibrosis. Gastroenterology. 2004 Jun 1;126(7):1740–9.

104. Woo G, Tomlinson G, Yim C, Lilly L, Therapondos G, Wong DKH, et al. Health state utilities and quality of life in patients with hepatitis B. Can J Gastroenterol [Internet]. 2012 [cited 2022 Feb 17];26(7):445. Available from: /pmc/articles/PMC3395446/

105. Che YH, You J, Chongsuvivatwong V, Li L, Sriplung H, Yan YZ, et al. Dynamics and liver disease specific aspects of quality of life among patients with chronic liver disease in Yunnan, China. Asian Pac J Cancer Prev [Internet]. 2014 [cited 2022 Feb 17];15(12):4765–71. Available from: https://pubmed.ncbi.nlm.nih.gov/24998539/

106. Saeed YA, Phoon A, Bielecki JM, Mitsakakis N, Bremner KE, Abrahamyan L, et al. A Systematic Review and Meta-Analysis of Health Utilities in Patients With Chronic Hepatitis C. Value Heal. 2020 Jan 1;23(1):127–37.

107. GSI - Data on file. Post-hoc Analyses: ALT Visualisation Graphs Week 48.

108. GSI - Data on file. NMA Report. 2022;

109. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Common Terminology Criteria for Adverse Events (CTCAE) v5.0 [Internet]. 2017 [cited 2022 Apr 12]. Available from: https://www.meddra.org/

110. ClinicalTrials.gov. Study to Assess Efficacy and Safety of Bulevirtide in Combination With Pegylated Interferon Alfa-2a in Participants With Chronic Hepatitis Delta (CHD) [Internet]. [cited 2022 Feb 25]. Available from: https://clinicaltrials.gov/ct2/show/NCT03852433

111. Urban S, Neumann-Haefelin C, Lampertico P. Hepatitis D virus in 2021: virology, immunology and new treatment approaches for a difficult-to-treat disease. Gut [Internet]. 2021 Sep 1 [cited 2022 Mar 31];70(9):1782–94. Available from: https://pubmed.ncbi.nlm.nih.gov/34103404/

112. Wedemeyer H, Yurdaydìn C, Dalekos GN, Erhardt A, Çakaloğlu Y, Değertekin H, et al. Peginterferon plus Adefovir versus Either Drug Alone for Hepatitis Delta. N Engl J Med [Internet]. 2011 Jan 26 [cited 2021 Aug 6];364(4):322–31. Available from: https://www.nejm.org/doi/10.1056/NEJMoa0912696

113. Frolov MY, Rogov VA, Salasyuk AS, Chulanov VP, Bogomolov PO. Clinical and economic aspects of bulevirtide use in patients with chronic hepatitis d. Infektsionnye Bolezn. 2020;18(2):104–11.

114. National Institute for Health and Care Excellence. Introduction | Developing NICE guidelines: the manual | Guidance | NICE [Internet]. 2022 [cited 2022 Apr 5]. Available from: https://www.nice.org.uk/process/pmg20/chapter/introduction

115. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. The reference case. 2013 [cited 2021 Aug 24]; Available from: https://www.nice.org.uk/process/pmg9/chapter/the-reference-case

116. Ossa D, Briggs A, Tafesse E, Iloeje U, Mukherjee J, Lozano-Ortega G, et al. Impact on Quality of Life of Health States Induced By Chronic Hepatitis B Infection: Estimates From Uninfected and Infected Persons in the UK. Value Heal [Internet]. 2005;8(6):A60. Available from: http://dx.doi.org/10.1016/S1098-3015(10)67323-8

117. Shepherd, J., Jones J, Baxter L, Gospodarevskaa E, Hartwell D, Harris P, Price A. Adefovir dipivoxil and pegylated interferon alpha for the treatment of chronic hepatitis B: An updated systematic review and economic evaluation. Health Technol Assess (Rockv). 2006;13(35).

118. Singh J, Longworth L. Comparison of methods for estimating contemporary costs: an application to liver transplantation in the United Kingdom. Int J Technol Assess Health Care. 2017;33(6):620–8.

119. The R Foundation. The R Project for Statistical Computing [Internet]. 2022. Available from: https://www.r-project.org/

120. Papatheodoridis G V., Chrysanthos N, Hadziyannis E, Cholongitas E, Manesis EK. Longitudinal changes in serum HBV DNA levels and predictors of progression during the natural course of HBeAg-negative chronic hepatitis B virus infection. J Viral Hepat. 2008;15(6):434–41.

121. Hsu YS, Chien RN, Yeh CT, Sheen IS, Chiou HY, Chu CM, et al. Long-term outcome after spontaneous HBeAg seroconversion in patients with chronic hepatitis B. Hepatology. 2002;35(6):1522–7.

122. Dakin H, Fidler C, Harper C. Mixed treatment comparison meta-analysis evaluating the relative efficacy of nucleos(t)ides for treatment of nucleos(t)ide-naive patients with chronic hepatitis B. Value Heal [Internet]. 2010;13(8):934–

45. Available from: http://dx.doi.org/10.1111/j.1524-4733.2010.00777.x

123. Zhou, K, Contag, C, Withaker, E and Terrault N. Spontaneous Loss of Surface Antigen among Adults Living with Chronic Hepatitis B Virus Infection: A Systematic Review and Pooled Meta-Analyses. Methods Mol Biol. 2019;176(5):139–48.

124. GSI - Data on file. Systematic Literature Review of HDV Biomarkers with Disease Progression. 2022.

125. Office for National Statistics. National life tables: UK [Internet]. 2021. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables

126. NICE. Guide to the methods of technology appraisal 2013 [Internet]. NICE; 2013 [cited 2017 Jan 23]. Available from: https://www.nice.org.uk/process/pmg9/chapter/foreword

127. Wolowacz SE, Briggs A, Belozeroff V, Clarke P, Doward L, Goeree R, et al. Estimating Health-State Utility for Economic Models in Clinical Studies: An ISPOR Good Research Practices Task Force Report. Value Heal. 2016;19(6):704–19.

128. Clarke PM, Gray AM, Briggs A, Stevens RJ, Matthews DR, Holman RR. Cost-utility analyses of intensive blood glucose and tight blood pressure control in type 2 diabetes (UKPDS 72). Diabetologia. 2005;48(5):868–77.

129. Spronk I, Polinder S, Bonsel GJ, Janssen MF, Haagsma JA. The relation between EQ-5D and fatigue in a Dutch general population sample: an explorative study. Health Qual Life Outcomes [Internet]. 2021;19(1):1–11. Available from: https://doi.org/10.1186/s12955-021-01771-3

130. Eriksson J, Kobelt G, Gannedahl M, Berg J. Association between Disability, Cognition, Fatigue, EQ-5D-3L Domains, and Utilities Estimated with Different Western European Value Sets in Patients with Multiple Sclerosis. Value Heal

[Internet]. 2019;22(2):231–8. Available from: https://doi.org/10.1016/j.jval.2018.08.002

131. GSI - Data on file. Meta-analyses of Health State Utilities in cHCV and cHBV. 2022.

132. Tolley K, Goad C, Yi Y, Maroudas P, Haiderali A, Thompson G. Utility elicitation study in the UK general public for late-stage chronic lymphocytic leukaemia. Eur J Health Econ. 2013 Oct;14(5):749–59.

133. Sullivan PW, Slejko JF, Sculpher MJ, Ghushchyan V. Catalogue of EQ-5D Scores for the United Kingdom. Med Decis Mak [Internet]. 2011 Nov 21 [cited 2018 Jan 17];31(6):800–4. Available from: http://journals.sagepub.com/doi/10.1177/0272989X11401031

134. Hagiwara Y, Shiroiwa T, Shimozuma K, Kawahara T, Uemura Y, Watanabe T, et al. Impact of Adverse Events on Health Utility and Health-Related Quality of Life in Patients Receiving First-Line Chemotherapy for Metastatic Breast Cancer: Results from the SELECT BC Study. Pharmacoeconomics [Internet]. 2018 Jan 30;36(2):215–23. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5805818/

135. NHS England. National Cost Collection: National Schedule of NHS costs - Year 2019-20 - NHS trust and NHS foundation trusts [Internet]. 2021. Available from: https://www.england.nhs.uk/national-cost-collection/#ncc1819

136. Crystallise. Heoro.com [Internet]. 2022. Available from: https://heoro.com/

137. Office for National Statistics. CPI WEIGHTS 06 : HEALTH [Internet]. Inflation and price indices. 2021. Available from: https://www.ons.gov.uk/economy/inflationandpriceindices/timeseries/chzw/mm23

138. National Institute for Health and Care Excellence. Tenofovir Disoproxil [Internet]. British National Formulary. 2022. Available from: https://bnf.nice.org.uk/medicinal-forms/tenofovir-disoproxil.html

139. Schneider P, McNamara S, Love-Koh J, Doran T, Gutacker N. Quality-adjusted life expectancy norms for the English population [Internet]. 2021. Available from: https://r4scharr.shinyapps.io/shortfall/

140. Hernandez Alava M, Pudney S, Wailoo A. Estimating the relationship between EQ-5D-5L and EQ-5D-3L: results from an English Population Study. 2020.

141. Cumpston M, Li T, Page MJ, Chandler J, Welch VA, Higgins JP, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. Cochrane database Syst Rev [Internet]. 2019 Oct 3 [cited 2022 Apr 5];10:ED000142. Available from: https://pubmed.ncbi.nlm.nih.gov/31643080/

142. National Institute for Health and Care Excellence. Clinical effectiveness | Single technology appraisal and highly specialised technologies evaluation: User guide for company evidence submission template | Guidance | NICE [Internet]. 2022 [cited 2022 Apr 5]. Available from: https://www.nice.org.uk/process/pmg24/chapter/clinical-effectiveness#quality-assessment-of-the-relevant-randomised-controlled-trials

143. Molinier L, Bauvin E, Combescure C, Castelli C, Rebillard X, Soulié M, et al. Methodological considerations in cost of prostate cancer studies: A systematic review. Value Heal [Internet]. 2008;11(5):878–85. Available from: http://dx.doi.org/10.1111/j.1524-4733.2008.00327.x

144. Stahmeyer JT, Becker H, Orlemann AL, Krauth C, Manns MP, Wedemeyer H, et al. HBV infections in Germany - care costs in a real-life setting HBV infections in Germany - health care costs in a real-life- setting Authors. 2017;1–8.

145. Buti M, Stepanova M, Palom A, Riveriro M, Esteban-Mur R. Hepatitis delta infection is associated with impairment of patient reported outcomes (PROS). Hepatol v70 suppl1 2019. 2019;70(Supplement 1):638A-639A.

146. Kumar P, Freeland C, Bodor S, Farrell S, Cohen C, Frasso R. Needs of

Individuals Living With Hepatitis Delta Virus and Their Caregivers, 2016–2019. Prev Chronic Dis [Internet]. 2020 [cited 2021 Oct 26];17:1–8. Available from: /pmc/articles/PMC7769086/

147. National Institute for Health and Care Excellence. Tenofovir disoproxil for the treatment of chronic hepatitis B | Committee papers | NICE. 2008;(December).

148. Caccamo L, Agnelli F, Reggiani P, Maggi U, Donato MF, Gatti S, et al. Role of lamivudine in the posttransplant prophylaxis of chronic hepatitis B virus and hepatitis delta virus coinfection. Transplantation. 2007;83(10):1341–4.

149. Goyal A, Romero-Severson EO. Screening for hepatitis D and PEG-Interferon over Tenofovir enhance general hepatitis control efforts in Brazil. PLoS One. 2018;13(9):1–17.

150. Wasuwanich P, Striley CW, Kamili S, Teshale EH, Seaberg EC, Karnsakul W. Hepatitis D-associated hospitalizations in the United States: 2010–2018. J Viral Hepat. 2022;29(3):218–26.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Bulevirtide for treating chronic hepatitis D [ID3732]

Clarification questions

June 2022

File name	Version	Contains confidential information	Date
ID3732_bulevirtide_CHD_clarification_response_v2.0 [ACIC]	2.0	Yes	17/06/2022

Section A: Clarification on effectiveness data

Results

A1. Priority question. The EAG has reviewed the MYR 301 trial data provided 12 May. These data indicate that not all patients who achieve response (particularly biochemical response) maintain it until week 48. Please provide data on the proportion of patients, at each study timepoint, with a response that was sustained until week 48. Please provide these data for both treatment arms, for the full trial population and the prior IFN-based therapy subgroup, and separately for virological response (undetectable HDV RNA or decrease by ≥ 2-log$_{10}$ IU/ml from baseline), biochemical response (ALT normalisation), and combined response (virological and biochemical response).

Company response: As the EAG have noted, in both the full trial population and the prior IFN-based therapy subgroup, not all patients who achieve ALT normalisation are observed to maintain it until Week 48 (Figure 1 and Figure 2). However, the data does show that an increasing number of participants demonstrate a biochemical response after 48 weeks. A further increase in responders is predicted at the interim 96-week data cut, which is expected to be made available in [redacted].

Figure 1: Proportion of biochemical responders in the full trial population (MYR 301)

Key: BLV: bulevirtide.
Notes: Percentages are based on the number of subjects within each treatment group. For missing values, the MEF approach was used.

Figure 2: Proportion of biochemical responders in the prior IFN-based therapy subgroup (MYR 301)

Key: BLV: bulevirtide.
Notes: Percentages are based on the number of subjects within each treatment group. For missing values, the MEF approach was used.

Furthermore, a sustained ALT response can be impacted by lifestyle choices, such as a reduction in alcohol consumption, or by the presence of concurrent liver conditions, such as fatty liver disease (1,2). Flares in ALT levels could alter the maintenance of a patient's biochemical response, despite treatment with bulevirtide. In addition, a flare in ALT levels could also explain why some virologic responders did not maintain a combined response through to Week 48 (Figure 3 and Figure 4).

Figure 3: Proportion of combined responders in the full trial population (MYR 301)

Key: BLV: bulevirtide.
Notes: Percentages are based on the number of subjects within each treatment group. For missing values, the MEF approach was used.

Figure 4: Proportion of combined responders in the prior IFN-based therapy subgroup (MYR 301)

Key: BLV: bulevirtide.
Notes: Percentages are based on the number of subjects within each treatment group. For missing values, the MEF approach was used.

While the maintenance of a biochemical and combined response has been observed across few patients treated with bulevirtide 2 mg, all patients with a virologic response maintained it until Week 48 (Figure 5 and Figure 6).

Figure 5: Proportion of virologic responders in full trial population (MYR 301)

Key: BLV: bulevirtide.

Notes: Percentages are based on the number of subjects within each treatment group. For missing values, the MEF approach was used.

Figure 6: Proportion of virlogic responders in the prior IFN-based therapy subgroup (MYR 301)

Key: BLV: bulevirtide.
Notes: Percentages are based on the number of subjects within each treatment group. For missing values, the MEF approach was used.

Data on the proportion of patients at each study timepoint for the full trial population can be found below in Tables 1-3, and for the prior IFN-based therapy subgroup in Tables 4-6.

Table 1: Frequency table for virologic response by visit in the full population (FAS; MYR 301)

	Delayed treatment (n=51)	BLV 2 mg (n=49)
Week 4		
Responder	[redacted]	[redacted]
Non-responder	[redacted]	[redacted]
Week 8		
Responder	[redacted]	[redacted]
Non-responder	[redacted]	[redacted]
Week 16		
Responder	[redacted]	[redacted]
Non-responder	[redacted]	[redacted]

Week 24		
Responder	2 (3.9%)	27 (55.1%)
Non-responder	49 (96.1%)	22 (44.9%)
Week 32		
Responder	[redacted]	[redacted]
Non-responder	[redacted]	[redacted]
Week 40		
Responder	[redacted]	[redacted]
Non-responder	[redacted]	[redacted]
Week 48		
Responder	[redacted]	[redacted]
Non-responder	[redacted]	[redacted]

Key: BLV: bulevirtide; FAS: full analysis set; MEF: missing equals failure.
Notes: Virologic response was defined as HDV RNA decrease by ≥2-$\log_{10}$ IU/mL or undetectable HDV RNA. Percentages are based on the number of subjects within each treatment group. For missing values, the MEF approach was used.

Table 2: Frequency table for ALT normalisation by visit in the full population (FAS; MYR 301)

	Delayed treatment (n=51)	**BLV 2 mg (n=49)**
Week 4		
Normal	[redacted]	[redacted]
Abnormal	[redacted]	[redacted]
Week 8		
Normal	[redacted]	[redacted]
Abnormal	[redacted]	[redacted]
Week 16		
Normal	[redacted]	[redacted]
Abnormal	[redacted]	[redacted]
Week 24		
Normal	3 (5.9%)	26 (53.1%)
Abnormal	48 (94.1%)	23 (46.9%)
Week 32		
Normal	[redacted]	[redacted]
Abnormal	[redacted]	[redacted]
Week 40		
Normal	[redacted]	[redacted]
Abnormal	[redacted]	[redacted]

Week 48		
Normal	[redacted]	[redacted]
Abnormal	[redacted]	[redacted]

Key: BLV: bulevirtide; FAS: full analysis set; MEF: missing equals failure.
Notes: Percentages are based on the number of subjects within each treatment group. For missing values, the MEF approach was used.

Table 3: Frequency table for combined response by visit in the full population (FAS; MYR 301)

	Delayed treatment (n=51)	BLV 2 mg (n=49)
Week 4		
Responder	[redacted]	[redacted]
Non-responder	[redacted]	[redacted]
Week 8		
Responder	[redacted]	[redacted]
Non-responder	[redacted]	[redacted]
Week 16		
Responder	[redacted]	[redacted]
Non-responder	[redacted]	[redacted]
Week 24		
Responder	0	17 (34.7%)
Non-responder	51 (100.0%)	32 (65.3%)
Week 32		
Responder	[redacted]	[redacted]
Non-responder	[redacted]	[redacted]
Week 40		
Responder	[redacted]	[redacted]
Non-responder	[redacted]	[redacted]
Week 48		
Responder	[redacted]	[redacted]
Non-responder	[redacted]	[redacted]

Key: BLV: bulevirtide; FAS: full analysis set; MEF: missing equals failure.
Notes: Percentages are based on the number of subjects within each treatment group. For missing values, the MEF approach was used.

Table 4: Frequency table for virologic response by visit in the prior IFN-based therapy subgroup (FAS; MYR 301)

	Delayed treatment (n=29)	BLV 2 mg (n=26)
Week 4		

Responder	[redacted]	[redacted]
Non-responder	[redacted]	[redacted]
Week 8		
Responder	[redacted]	[redacted]
Non-responder	[redacted]	[redacted]
Week 16		
Responder	[redacted]	[redacted]
Non-responder	[redacted]	[redacted]
Week 24		
Responder	[redacted]	[redacted]
Non-responder	[redacted]	[redacted]
Week 32		
Responder	[redacted]	[redacted]
Non-responder	[redacted]	[redacted]
Week 40		
Responder	[redacted]	[redacted]
Non-responder	[redacted]	[redacted]
Week 48		
Responder	[redacted]	[redacted]
Non-responder	[redacted]	[redacted]

Key: BLV: bulevirtide; FAS: full analysis set; MEF: missing equals failure.
Notes: Virologic response was defined as HDV RNA decrease by ≥2-$\log_{10}$ IU/mL or undetectable HDV RNA. Percentages are based on the number of subjects within each treatment group. For missing values, the MEF approach was used.

Table 5: Frequency table for ALT normalisation by visit in the prior IFN-based therapy subgroup (FAS; MYR 301)

	Delayed treatment (n=29)	BLV 2 mg (n=26)
Week 4		
Normal	[redacted]	[redacted]
Abnormal	[redacted]	[redacted]
Week 8		
Normal	[redacted]	[redacted]
Abnormal	[redacted]	[redacted]
Week 16		
Normal	[redacted]	[redacted]
Abnormal	[redacted]	[redacted]
Week 24		

Normal	[redacted]	[redacted]
Abnormal	[redacted]	[redacted]
Week 32		
Normal	[redacted]	[redacted]
Abnormal	[redacted]	[redacted]
Week 40		
Normal	[redacted]	[redacted]
Abnormal	[redacted]	[redacted]
Week 48		
Normal	[redacted]	[redacted]
Abnormal	[redacted]	[redacted]

Key: BLV: bulevirtide; FAS: full analysis set; MEF: missing equals failure.
Notes: Percentages are based on the number of subjects within each treatment group. For missing values, the MEF approach was used.

Table 6: Frequency table for combined response by visit in the prior IFN-based therapy subgroup (FAS; MYR 301)

	Delayed treatment (n=29)	BLV 2 mg (n=26)
Week 4		
Responder	[redacted]	[redacted]
Non-responder	[redacted]	[redacted]
Week 8		
Responder	[redacted]	[redacted]
Non-responder	[redacted]	[redacted]
Week 16		
Responder	[redacted]	[redacted]
Non-responder	[redacted]	[redacted]
Week 24		
Responder	[redacted]	[redacted]
Non-responder	[redacted]	[redacted]
Week 32		
Responder	[redacted]	[redacted]
Non-responder	[redacted]	[redacted]
Week 40		
Responder	[redacted]	[redacted]
Non-responder	[redacted]	[redacted]
Week 48		

Responder	[redacted]	[redacted]
Non-responder	[redacted]	[redacted]

Key: BLV: bulevirtide; FAS: full analysis set; MEF: missing equals failure.
Notes: Percentages are based on the number of subjects within each treatment group. For missing values, the MEF approach was used.

A2. Priority question. The MYR 301 response data provided on 12 May also show that a larger proportion of patients in the delayed treatment arm achieve a biochemical response than achieve a virological response at most timepoints. Please provide a clinical rationale for the observed data.

Company response: In accordance with the NAs mechanism of action, there is no effect on HDV replication, and as such any improvement in ALT levels would lead to a greater biochemical response relative to virologic response amongst participants in the delayed treatment arm (3–5).

ALT is impacted by a number of different factors and lifestyle choices, for example reduced alcohol consumption can impact ALT levels even in the absence of HDV treatment. Moreover, in the MYR 301 clinical study, patients were allowed to take NAs (e.g., TDF) if indicated in accordance with the current to EASL/AASLD guidelines (3–5).

A3. Priority question. The EAG's clinical experts have advised that patients achieving a virological response are likely to also achieve a biochemical response unless there are other reasons for abnormal ALT levels. Please provide the possible clinical reasons for the lack of ALT normalisation for patients with only virological response at week 48 in MYR 301.

Company response: Gilead concurs that a virologic response is often associated with the normalisation of ALT. Across the MYR clinical study programme, ALT reductions were observed across most participants. It is well documented in viral hepatitis that other factors (e.g., steatosis) can often prevent patients from achieving normalised ALT (6).

As evidenced in Figure 7 below, in the bulevirtide 2 mg treatment arm, [redacted] subjects ([redacted]) who showed a virologic response at Week 24 experienced a combined response at Week 48, while [redacted] subjects ([redacted]) continued to show a virologic response at Week 48.

Figure 7: Evolution of response amongst patients from Week 24 to Week 48 in the bulevirtide 2 mg treatment group (MYR 301)

Key: ALT: alanine aminotransferase; CR: combined response; NR: non-response; VR: virologic response; W24: Week 24; W48: Week 48.

The combined response endpoint is based upon interim 48-week data. An interim 96-week data cut is expected to be made available in [redacted], which is expected to provide further evidence as to the optimal time to assess treatment response. Despite this uncertainty, a large proportion of patients showed a [redacted] in ALT levels after 48 weeks of bulevirtide 2 mg monotherapy. Figure 8 below (Figure 29, Appendix N) visualises the evolution of ALT improvement for virologic responders, demonstrating [redacted]. Therefore, patients with a virologic response still experienced a clinical benefit, despite the threshold for ALT normalisation not being met.

Figure 8: Evolution of ALT response over 48 weeks in patients showing a virologic response in the bulevirtide 2 mg treatment group (MYR 301)

Key: ALT: alanine aminotransferase; BLV: bulevirtide; ULN: upper limit of normal.
Notes: ULN = 40 IU/L. Virologic responder population represents [redacted] subjects in the bulevirtide 2 mg treatment arm.
Source: Data on file (7).

A4. Priority question. Please provide results for the difference (in proportions, reported as % (95% CI)) between treatment arms for the primary outcome (combined response) and HDV RNA decrease by ≥2-log$_{10}$ IU/mL or undetectable HDV RNA for the full trial population in the MYR 301 trial at weeks 24 and 48. This has already been provided for some outcomes (for example, ALT normalisation in Table 15 of the submission), but is not consistently provided for all outcomes.

Company response: Results for the difference (in proportions, reported as % (95% CI)) between treatment arms for the primary outcome (combined response) and HDV RNA decrease by ≥2-log10 IU/mL or undetectable HDV RNA for the full trial population in the MYR 301 trial at Weeks 24 and 48 are provided below in Table 7 and Table 8.

Table 7: Achievement of combined response at Weeks 24 and 48 (FAS; MYR 301)

	Delayed Treatment (n=51)	BLV 2 mg (n=49)
Week 24		
Number of subjects included in analysis	51	49
Number of responders	0	18
Proportion of responders, % (95% CI)	0 [redacted]	36.7 [redacted]
Difference in proportions, % (99% CI)	—	36.7 [redacted]
p value	—	[redacted]
Week 48		
Number of subjects included in analysis	[redacted]	[redacted]
Number of responders	[redacted]	[redacted]
Proportion of responders, % (95% CI)	[redacted]	[redacted]
Difference in proportions, % (96% CI)	—	[redacted]
p value	—	[redacted]

Key: BLV: bulevirtide; CI: confidence interval; FAS: full analysis set; LOCF: last observation carried forward; MEF: missing equals failure.
Notes: A confidence level of 95% is used for within group CIs. For difference in proportions, the confidence level used was 99% for 24 weeks (Week 24 interim analysis) and 96% for Week 48 (Week 48 primary endpoint analysis). Fisher's exact tests were used for each comparison of BLV 2 mg versus delayed treatment using a significance level of 0.01 at Week 24 and 0.04 at Week 48. For missing values, the LOCF approach was used if COVID-19 related, and the MEF approach otherwise.
Source: Table 12, MYR 301 CSR (8).

Table 8: HDV RNA decrease by ≥2-log$_{10}$ IU/mL or undetectable HDV RNA at Weeks 24 and 48 (FAS; MYR 301)

	Delayed Treatment (n=51)	BLV 2 mg (n=49)
Week 24		
Number of subjects included in analysis	51	49
Number of responders	[redacted]	[redacted]
Proportion of responders, % (95% CI)	[redacted]	[redacted]
Difference in proportions, % (95% CI)	—	[redacted]
p value	—	[redacted]
Week 48		
Number of subjects included in analysis	51	49
Number of responders	[redacted]	[redacted]
Proportion of responders, % (95% CI)	[redacted]	[redacted]
Difference in proportions, % (95% CI)	—	[redacted]
p value	—	[redacted]

Key: BLV: bulevirtide; CI: confidence interval; FAS: full analysis set.
Notes: A confidence level of 95% is used for within group CIs and for CIs in different proportions. Fisher's exact tests were used for each comparison of BLV 2 mg versus delayed treatment using a significance level of 0.05.
Source: Ad Hoc Table 10922.1, MYR 301 CSR (8).

A5. Priority question. The EAG considers the full trial population to be more relevant and more robust than the subgroup of patients who had previously had IFN-based therapy for the following reasons: The full trial population provides a larger sample size, it includes patients who were intolerant of or for whom IFN-based therapy was contraindicated, the subgroup analysis by prior IFN-based therapy does not indicate a difference in efficacy between the subgroups, and the trial was not stratified by prior TNF-based therapy at randomisation. Please provide a more detailed rationale for focusing on the subgroup of patients who had had prior TNF-based therapy in the economic model.

Company response: In acknowledgement of the points made, Gilead are aligned with the EAG in the use of the full trial population in the economic model and have implemented this as part of the clarification response (Table 19).

A6. Priority question. Please provide the baseline characteristics for the prior IFN-based therapy subgroup of MYR 301.

Company response: The baseline characteristics for the prior IFN-based therapy subgroup of MYR 301 can be found in Table 9 below.

Table 9: Patient demographics and baseline characteristics of the prior IFN-based therapy subgroup of MYR 301 (FAS; MYR 301)

	Delayed treatment (n=29)	BLV 2 mg (n=26)
Sex (n, %)		
Male	[redacted]	[redacted]
Female	[redacted]	[redacted]
Age (Years)		
Mean (SD)	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Median (IQR)	[redacted]	[redacted]
Race, n (%)		
White	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]
Asian	[redacted]	[redacted]
BMI (kg/m^2), n (%)		
Mean (SD)	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Median (IQR)	[redacted]	[redacted]
BMI Categories, n (%)		
<30 kg/m2	[redacted]	[redacted]
≥30 kg/m2	[redacted]	[redacted]
Cirrhosis Status, n (%)		
Present	[redacted]	[redacted]
Absent	[redacted]	[redacted]
Child-Pugh Score		
Mean (SD)	[redacted]	[redacted]
Median (IQR)	[redacted]	[redacted]
Child-Pugh Class, n (%)		
A	[redacted]	[redacted]
HDV Genotype, n (%)		
HDV Genotype 1	[redacted]	[redacted]
HDV Genotype 5	[redacted]	[redacted]
HBV Genotype, n (%)		

Genotype A	[redacted]	[redacted]
Genotype D	[redacted]	[redacted]
Genotype E	[redacted]	[redacted]
No data	[redacted]	[redacted]
HBV DNA (log_{10} IU/mL)		
n/nmiss	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
HDV RNA (log_{10} IU/mL)		
n/nmiss	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
HBeAg Status, n (%)		
Negative	[redacted]	[redacted]
HBsAg (log_{10} IU/mL)		
n/nmiss	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
ALT (U/L)		
Mean (SD)	[redacted]	[redacted]

Key: ALT: alanine aminotransferase; BLV: bulevirtide; BMI: body mass index; HBeAg: hepatitis B e surface antigen: HBsAg: hepatitis b surface antigen; HBV: hepatitis B virus; HDV: hepatitis delta virus; IFN: interferon; IQR: interquartile range; n/nmiss: number of participants with evaluable/missing data; Q1: first quartile; Q3: third quartile.
Notes: Child-Pugh score and class are presented for cirrhotic patients only, with percentages based on the number of cirrhotic subjects. Assessments of liver fibrosis were performed only for those subjects who consented to undergo a liver biopsy at baseline and Week 48. Percentages were based on the number of subjects within each treatment group.

A7. Priority question. Please provide results for EQ-5D-3L utility scores from the MYR301 trial at baseline and 48-weeks (similar to the format in the Gilead Data on File - MYR 301 W48 analysis_EQ-5D analysis report) for the subgroups of patients with and without prior IFN-based treatment.

Company response: In line with the response to A5 and considering the full trial population is now to be used in the model as preferred by the EAG, this question is no longer relevant.

A8. Priority question. Please provide the baseline characteristics for the cirrhotic and non-cirrhotic subgroup in MYR 301, and the results at week 48 for the secondary outcomes of HDV RNA decrease by ≥2-log_{10} IU/mL or undetectable HDV RNA and ALT normalisation (currently only data for

combined response in the MYR301 trial is reported for each subgroup in Appendix E).

Company response: The baseline characteristics for the cirrhotic and non-cirrhotic subgroups in MYR 301 are presented in Table 10 and Table 11 respectively.

Table 10: Patient demographics and baseline characteristics of the cirrhotic subgroup of MYR 301 (FAS; MYR 301)

	Delayed treatment (n=24)	BLV 2 mg (n=23)
Sex (n, %)		
Male	[redacted]	[redacted]
Female	[redacted]	[redacted]
Age (Years)		
Mean (SD)	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Median (IQR)	[redacted]	[redacted]
Race, n (%)		
White	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]
Asian	[redacted]	[redacted]
BMI (kg/m^2), n (%)		
Mean (SD)	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Median (IQR)	[redacted]	[redacted]
BMI Categories, n (%)		
<30 kg/m^2	[redacted]	[redacted]
≥30 kg/m^2	[redacted]	[redacted]
Child-Pugh Score		
Mean (SD)	[redacted]	[redacted]
Median (IQR)	[redacted]	[redacted]
Child-Pugh Class, n (%)		
A	[redacted]	[redacted]
HDV Genotype, n (%)		
HDV Genotype 1	[redacted]	[redacted]
HDV Genotype 5	[redacted]	[redacted]

HBV Genotype, n (%)		
Genotype A	[redacted]	[redacted]
Genotype D	[redacted]	[redacted]
Genotype E	[redacted]	[redacted]
No data	[redacted]	[redacted]
HBV DNA (log_{10} IU/mL)		
n/nmiss	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
HDV RNA (log_{10} IU/mL)		
n/nmiss	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
HBeAg Status, n (%)		
Negative	[redacted]	[redacted]
HBsAg (log_{10} IU/mL)		
n/nmiss	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
ALT (U/L)		
Mean (SD)	[redacted]	[redacted]

Key: ALT: alanine aminotransferase; BLV: bulevirtide; BMI: body mass index; HBeAg: hepatitis B e surface antigen: HBsAg: hepatitis b surface antigen; HBV: hepatitis B virus; HDV: hepatitis delta virus; IFN: interferon; IQR: interquartile range; n/nmiss: number of participants with evaluable/missing data; Q1: first quartile; Q3: third quartile.
Notes: Child-Pugh score and class are presented for cirrhotic patients only, with percentages based on the number of cirrhotic subjects. Assessments of liver fibrosis were performed only for those subjects who consented to undergo a liver biopsy at baseline and Week 48. Percentages were based on the number of subjects within each treatment group.

Table 11: Patient demographics and baseline characteristics of the non-cirrhotic subgroup of MYR 301 (FAS; MYR 301)

	Delayed treatment (n=27)	BLV 2 mg (n=26)
Sex (n, %)		
Male	[redacted]	[redacted]
Female	[redacted]	[redacted]
Age (Years)		
Mean (SD)	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Median (IQR)	[redacted]	[redacted]
Race, n (%)		
White	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]
Asian	[redacted]	[redacted]
BMI (kg/m^2), n (%)		
Mean (SD)	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Median (IQR)	[redacted]	[redacted]
BMI Categories, n (%)		
<30 kg/m^2	[redacted]	[redacted]
≥30 kg/m^2	[redacted]	[redacted]
Child-Pugh Score		
Mean (SD)	[redacted]	[redacted]
Median (IQR)	[redacted]	[redacted]
Child-Pugh Class, n (%)		
A	[redacted]	[redacted]
HDV Genotype, n (%)		
HDV Genotype 1	[redacted]	[redacted]
HDV Genotype 5	[redacted]	[redacted]
HBV Genotype, n (%)		
Genotype A	[redacted]	[redacted]
Genotype D	[redacted]	[redacted]
Genotype E	[redacted]	[redacted]

No data	[redacted]	[redacted]
HBV DNA (log_{10} IU/mL)		
n/nmiss	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
HDV RNA (log_{10} IU/mL)		
n/nmiss	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
HBeAg Status, n (%)		
Negative	[redacted]	[redacted]
HBsAg (log_{10} IU/mL)		
n/nmiss	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
ALT (U/L)		
Mean (SD)	[redacted]	[redacted]

Key: ALT: alanine aminotransferase; BLV: bulevirtide; BMI: body mass index; HBeAg: hepatitis B e surface antigen: HBsAg: hepatitis b surface antigen; HBV: hepatitis B virus; HDV: hepatitis delta virus; IFN: interferon; IQR: interquartile range; n/nmiss: number of participants with evaluable/missing data; Q1: first quartile; Q3: third quartile.
Notes: Child-Pugh score and class are presented for cirrhotic patients only, with percentages based on the number of cirrhotic subjects. Assessments of liver fibrosis were performed only for those subjects who consented to undergo a liver biopsy at baseline and Week 48. Percentages were based on the number of subjects within each treatment group.

The proportion of patients showing a virologic response at Week 48 was consistent between patients with and without cirrhosis in the bulevirtide 2 mg treatment arm. At Week 48, [redacted] of 23 subjects ([redacted]) with cirrhosis and [redacted] of 26 subjects ([redacted]) without cirrhosis experienced a virologic response. In the delayed treatment arm, the virologic response rate observed was minimal and was consistent across patients with and without cirrhosis (Table 12).

Table 12: HDV RNA decrease by ≥2-log_{10} IU/mL or undetectable HDV RNA at Week 48 by cirrhosis status subgroup (FAS; MYR 301)

	Delayed Treatment (n=51)	**BLV 2 mg (n=49)**
With cirrhosis, n	**24**	**23**
Responder, n (%)	[redacted]	[redacted]
Non-responder, n (%)	[redacted]	[redacted]
Without cirrhosis, n	**27**	**26**
Responder, n (%)	[redacted]	[redacted]
Non-responder, n (%)	[redacted]	[redacted]

Key: BLV: bulevirtide; FAS: full analysis set; MEF: missing equals failure.
Notes: Percentages are based on the number of subjects within each treatment group. For missing values, the MEF approach was used.

The proportion of subjects achieving normal ALT levels at Week 48 was greater in patients without cirrhosis, compared to those with cirrhosis. At Week 48, [redacted] of 23 subjects ([redacted]) with cirrhosis demonstrated normal ALT levels after treatment with bulevirtide 2 mg, compared with [redacted] of 24 subjects ([redacted]) without cirrhosis. The proportion of patients with normal ALT levels in the delayed treatment arm was similar amongst patients with and without cirrhosis (see Table 13).

Table 13: ALT normalisation at Week 48 by cirrhosis status subgroup (FAS; MYR 301)

	Delayed Treatment (n=51)	**BLV 2 mg (n=49)**
With cirrhosis, n	**24**	**23**
Normal, n (%)	[redacted]	[redacted]
Abnormal, n (%)	[redacted]	[redacted]
Without cirrhosis, n	**27**	**26**
Normal, n (%)	[redacted]	[redacted]
Abnormal, n (%)	[redacted]	[redacted]

Key: ALT: alanine aminotransferase; BLV: bulevirtide; FAS: full analysis set; MEF: missing equals failure.
Notes: Percentages are based on the number of subjects within each treatment group. For missing values, the MEF approach was used.
Source: Table 14.2.2.2-5 and Table 14.2.2.2-7, MYR 301 CSR (8).

A9. Priority question. Table 17 of the MYR 301 CSR shows the change in fibrosis stage from baseline to week 48. Please explain the large proportion of patients with an improvement in METAVIR fibrosis stage in the delayed treatment arm (38.5%) and the low proportion of patients with a virological response (3.9%) in the same arm.

Company response: Patients in the delayed treatment arm did not receive HDV treatment, but were allowed to continue ongoing anti-HBV treatment with NAs to treat the underlying CHB infection. Long-term NA therapy can result in a significant improvement of histological necroinflammation and fibrosis in patients with CHB (5). However, while NAs strongly suppress HBV replication, they have little effect on HBsAgs and as such have no effect on HDV replication (9).

In MYR 301, a majority of participants had FibroScan® measurements at baseline, Week 24, and Week 48 to assess the extent of liver stiffness as a surrogate measure of fibrosis. Data shows that there was a [redacted] kPa increase in liver stiffness in the delayed treatment arm, while in the bulevirtide 2 mg treatment group, a [redacted] kPa

decrease in liver stiffness was observed, suggesting that bulevirtide had a meaningful impact on liver stiffness.

A10. Priority question. Please provide the results of the virology resistance analysis summarised in the virology study report mentioned in the CSR for MYR 301.

Company response: Resistance analysis was performed on [redacted] participants who experienced virologic breakthrough (VB, defined as 2 consecutive increases in HDV RNA of ≥1 log_{10} IU/mL from nadir or 2 consecutive HDV RNA values ≥LLOD if previously <LLOD; [redacted] participants) or HDV RNA decline <1 log10 IU/mL (non-responders; 6 participants) at Week 48, with [redacted] and [redacted] participants in the bulevirtide 2 mg and 10 mg groups, respectively. No amino acid substitutions at HBV N-terminal of PreS1 domain covering bulevirtide sequence positions (PreS1 bulevirtide region) or HDV HDAg associated with reduced susceptibility to bulevirtide were identified in the isolates from any of these [redacted] participants at baseline and Week 48. In addition, the bulevirtide EC50 values from [redacted] baseline samples from participants of this study were found to be similar across non-responders, partial responders (HDV RNA decline ≥1 but <2 log_{10} IU/mL at Week 48) and virologic responders (<LLOD or a decline in HDV RNA ≥2 log_{10} IU/mL at Week 48) regardless of the presence of HBV and HDV polymorphisms.

In summary, no evidence of resistance was found; no amino acid substitutions at HBV at PreS1 bulevirtide region and HDAg associated with reduced susceptibility to bulevirtide were detected at baseline and throughout 48 weeks of treatment.

A11. Please provide results for the TDF group in Table 32 of the submission for MYR202, as currently the table only includes the three BLV arms.

Company response: The most common AEs reported for the TDF treatment group in MYR 202 can be found in Table 14 below.

Table 14: Most common AEs reported by subjects (SAS; MYR 202)

	TDF (n=28)	BLV 2 mg + TDF (n=28)	BLV 5 mg + TDF (n=32)	BLV 10 mg + TDF (n=30)	BLV total (n=90)
Subjects with any AE, n (%)	**14 (50.0)**	**18 (64.3)**	**21 (65.6)**	**23 (76.7)**	**62 (68.9)**

Total bile acids increased	6 (21.4)	8 (28.6)	12 (37.5)	15 (50.0)	35 (38.9)
ALT increased	4 (14.3)	4 (14.3)	7 (21.9)	9 (30.0)	20 (22.2)
AST increased	3 (10.7)	3 (10.7)	7 (21.9)	8 (26.7)	18 (20.0)
Thrombocytopenia	3 (10.7)	3 (10.7)	5 (15.6)	2 (6.7)	10 (11.1)
Fatigue	2 (7.1)	1 (3.6)	2 (6.3)	5 (16.7)	8 (8.9)
Nausea	0 (0.0)	1 (3.6)	4 (12.5)	3 (10.0)	8 (8.9)
Neutropenia	3 (10.7)	1 (3.6)	4 (12.5)	0 (0.0)	5 (5.6)
Dizziness	0 (0.0)	2 (7.1)	2 (6.3)	3 (10.0)	7 (7.8)
Headache	0 (0.0)	2 (7.1)	2 (6.3)	3 (10.0)	7 (7.8)
Leukopenia	1 (3.6)	4 (14.3)	2 (6.3)	0 (0.0)	6 (6.7)
GGT increased	3 (10.7)	0 (0.0)	1 (3.1)	2 (6.7)	3 (3.3)
Lymphopenia	0 (0.0)	3 (10.7)	0 (0.0)	0 (0.0)	3 (3.3)

Key: AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyltransferase; SAS: safety analysis set.
Notes: Percentages are based on the number of participants within each treatment group.
Source: Table 45, MYR 202 CSR (10).

A12. Please provide a breakdown of the grade 2 and grade 3 AEs in the two treatment arms in MYR 301, similar to Table 29 in the submission but without limiting the list to more common (>5%) AEs.

Company response: A breakdown of the Grade 2 and Grade 3 AEs in the bulevirtide 2 mg and 10 mg treatment arms can be found in Table 15 and Table 16 below.

Table 15: TEAEs of Grade 2 or higher by preferred term reported in the bulevirtide treatment groups by Week 48 (SAS; MYR 301)

TEAE by Preferred Term	BLV 2 mg (n=49)	BLV 10 mg (n=50)
Subjects with any Grade 2 TEAE or above, n (%)	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Angina pectoris	[redacted]	[redacted]
Blepharitis	[redacted]	[redacted]
Abdominal distension	[redacted]	[redacted]

Abdominal pain	[redacted]	[redacted]
Abdominal pain upper	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Chest pain	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Injection site erythema	[redacted]	[redacted]
Injection site irritation	[redacted]	[redacted]
Injection site pruritus	[redacted]	[redacted]
Injection site reaction	[redacted]	[redacted]
Malaise	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]
Hyperbilirubinaemia	[redacted]	[redacted]
Pharyngitis	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]
COVID-19 pneumonia	[redacted]	[redacted]
Anterobiasis	[redacted]	[redacted]
Injection site abscess	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]
Respiratory tract infection viral	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
Foot fracture	[redacted]	[redacted]
Meniscus injury	[redacted]	[redacted]
Radius fracture	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]
GGT increased	[redacted]	[redacted]
Lipase increased	[redacted]	[redacted]
WBC count decreased	[redacted]	[redacted]
Activated partial thromboplastin time prolonged	[redacted]	[redacted]
Amylase increased	[redacted]	[redacted]
Blood bilirubin increased	[redacted]	[redacted]
Lymphocyte count increased	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]

Vitamin D deficiency	[redacted]	[redacted]
Hypercreatininaemia	[redacted]	[redacted]
Hypophosphataemia	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Bone pain	[redacted]	[redacted]
Osteopenia	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Depression	[redacted]	[redacted]
Haematuria	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]
Angioedema	[redacted]	[redacted]
Toxic skin eruption	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
Varicose vein	[redacted]	[redacted]

Key: BLV: bulevirtide; GGT: gamma-glutamyltransferase; SAS: safety analysis set; TEAE: treatment emergent adverse event.
Notes: Treatment-emergent events began on or after the study drug start date up to 30 days after the permanent discontinuation of the study drug, or led to premature study drug discontinuation. Severity grades were defined by CTCAM 5.0.
Source: Table 1.1.4, MYR 301 CSR (8).

Table 16: TEAEs of Grade 3 or higher by preferred term reported in the bulevirtide treatment groups by Week 48 (SAS; MYR 301)

TEAE by Preferred Term	BLV 2 mg (n=49)	BLV 10 mg (n=50)
Subjects with any Grade 3 TEAE or above, n (%)	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]
COVID-19 pneumonia	[redacted]	[redacted]
Depression	[redacted]	[redacted]
Foot fracture	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]
Osteopenia	[redacted]	[redacted]

Key: BLV: bulevirtide; SAS: safety analysis set; TEAE: treatment emergent adverse event.
Notes: Treatment-emergent events began on or after the study drug start date up to 30 days after the permanent discontinuation of the study drug, or led to premature study drug discontinuation. Severity grades were defined by CTCAM 5.0.
Source: Table 1.1.3.2, MYR 301 CSR (8).

A13. Please confirm for how many patients in each treatment arm that LOCF was used due to COVID in MYR 301.

Company response: The total number of patients in each treatment arm where LOCF was used due to COVID-19 can be found below in Table 17.

Table 17: LOCF at Weeks 24 and 48 due to COVID-19

	Delayed treatment (n=51)	BLV 2 mg (n=49)	BLV 10 mg (n=50)
Week 24	[redacted]	[redacted]	[redacted]
Week 48	[redacted]	[redacted]	[redacted]

Key: BLV: bulevirtide; FAS: full analysis set; LOCF: last observation carried forward.
Notes: Percentages are based on the number of subjects within each treatment group.
Source: Table 14.1.2-3, MYR 301 CSR (8).

A14. Please clarify why treatment with bulevirtide should be stopped for patients who develop decompensated cirrhosis or HCC.

Company response: In July 2020, bulevirtide received conditional marketing authorisation from the European Medicines Agency (EMA) for the treatment of chronic hepatitis delta virus (HDV) infection in plasma (or serum) HDV-RNA positive adult patients with compensated liver disease. Conditional marketing authorisation was granted based on surrogate endpoint data from two Phase 2 studies, namely MYR 202 and MYR 203 (11). Across both studies, participants who had current or previous decompensated liver disease, or any previous or current malignant neoplasms including HCC, were not eligible according to the exclusion criteria (10,12). Similar exclusion criteria regarding patients with decompensated cirrhosis or HCC was also applied to the ongoing pivotal MYR 301 clinical study (8). Therefore, patients with decompensated cirrhosis and HCC were not included in the clinical development programme.

Given that the pharmacokinetics, safety and efficacy of bulevirtide has not been established in patients with decompensated cirrhosis, the SmPC does not recommend the use of bulevirtide in this patient population (13).

A15. Please provide pdfs of all the studies included in the Systematic Literature Review of HDV Biomarkers with Disease Progression (see Table 2 of Data on File report)

1. **Please clarify how people in these studies who were HDV-RNA negative (or undetectable) had achieved this. What proportion of patients had received IFN-based therapy**?

Company response: PDFs of all studies included in the Systematic Literature Review of HDV Biomarkers with Disease Progression are provided in the submitted materials. However, the data requested in A15.1 was not extracted during the SLR, and therefore cannot be provided given the timeframe for response.

Additional clarification questions:

A16. Priority question: The tables 10979.1, 10979.4 and 10979.5 from the MYR 301 CSR provide METAVIR fibrosis scores at baseline and at Week 48 for the overall trial population and patients with and without cirrhosis at baseline. The EAG has collated these data into a single table, provided below. Please confirm that the EAG has interpreted the data correctly?

Arm	METAVIR fibrosis score at baseline					
	F0	F1	F2	F3	F4	Missing
Non-cirrhotic patients						
Delayed Treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bulevirtide 2 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cirrhotic patients						
Delayed Treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bulevirtide 2 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Overall						
Delayed Treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bulevirtide 2 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Sources: CSR, Ad Hoc Tables 10979.1, 10979.3 and 10979.4

Company response: Gilead can confirm that the EAG has interpreted the data from Tables 10979.1, 10979.3, and 10979.4 correctly.

A17. Priority question: The EAG noticed that, according to Table 10979.3 in the CSR, many patients in the cirrhosis subgroup had baseline METAVIR stages of F0-F3. According to the METAVIR staging, F4 is the only stage corresponding to cirrhosis. Please explain how cirrhosis was defined in the trial, at screening, baseline and during follow-up?

Company response: In MYR 301, the cirrhosis status of patients at screening, baseline, and follow-up, was determined according to the clinical judgement of the investigators. There is currently not a confirmed definition of cirrhosis in HDV, so investigators used clinical, histological (e.g., METAVIR, Ishak, and Knodell fibrosis scores) and other diagnostic measures (e.g., FibroScan®) to confirm the presence or absence of cirrhosis.

A18. Priority question: Based on these data, [redacted] of participants in the delayed treatment arm and [redacted] of participants in the bulevirtide 2 mg arm had a baseline METAVIR fibrosis stage of F0 or F1. How does the company believe this affects the generalisability of the MYR 301 trial data to the population outlined in the decision problem, i.e., patients with a METAVIR fibrosis score of F2 or above?

a. **Please discuss what the expected impact is likely to be on treatment response?**

b. **Using threshold analysis on treatment response in the model, please test the impact on the cost-effectiveness results.**

Company response: In the MYR 301 clinical study, [redacted] of patients ([redacted] of 51 subjects) in the delayed treatment arm, and [redacted] of patients ([redacted] of 49 subjects) in the bulevirtide 2 mg treatment arm, had cirrhosis at the time of enrolment based on clinical assessments by the study investigators. Liver fibrosis assessments were performed at baseline and Week 48 for patients that consented to undergo a liver biopsy. Liver biopsy data was unavailable for [redacted] of patients in both the delayed treatment arm ([redacted] of 51 subjects) and the bulevirtide 2 mg treatment group ([redacted] of 49 subjects), whilst patients with a liver biopsy performed within one year prior to

study enrolment did not require a further biopsy procedure. Gilead does not foresee an impact on the generalisability of the MYR 301 trial data to the population outlined in the decision problem. From baseline to Week 48, patients receiving bulevirtide 2 mg demonstrated an improvement in fibrosis and necroinflammation compared to the patients in the delayed treatment group, regardless of fibrosis staging.

Gilead are still awaiting confirmation from the EAG on the thresholds required for the threshold analysis on treatment response in the model. On this basis, we propose that this can be explored at technical engagement.

A19. Priority question: Please provide the baseline ALT levels separately for participants with METAVIR fibrosis scores F0, F1, F2, F3, and F4 in MYR 301.

Company response: In the MYR 301 clinical study, assessments of liver fibrosis were performed only for participants who consented to undergo a liver biopsy at baseline and Week 48. As a result, METAVIR fibrosis scores were collected for only [redacted] of 150 subjects ([redacted]) in the MYR 301 study population. As represented in A16, the number of patients across each METAVIR fibrosis score at baseline is limited, and thus making robust comparisons between each category is challenging.

Furthermore, such a comparison would also have to consider the gender difference in ALT levels, and a difference in the definition of ALT normalisation according to study site. This would reduce the sample size across each METAVIR fibrosis score further. Gilead therefore does not consider a comparison of ALT levels between METAVIR fibrosis scores to be appropriate.

A20. Priority question: If possible, please provide the response rates for, virologic, biological, and combined response for each METAVIR fibrosis stage separately?

Company response: See response to A19.

ALT normalisation data

A21. Priority question: The company has provided the EAG with baseline ALT normalisation data in both Figure 29 of Appendix N, 'Post-hoc analysis of ALT response', and in the additional data provided on the 12th May in the plots of the data extrapolation. These data appear inconsistent. At baseline in Figure

29, [redacted] virologic response patients from bulevirtide 2 mg are presented as having ALT levels within the upper limit of normal, i.e. meeting the criteria for biochemical response. However, in the overall population graph for bulevirtide 2 mg for ALT normalisation from May 12th, [redacted] are reported as having ALT normalisation at baseline (left: ALT response extrapolation data; right: Figure 29, Appendix N). It appears two thresholds have been used to define ALT normalisation in the CS, 1) ≤ 31 U/L for females and ≤ 41 U/L for males in Russia and ≤ 34 U/L for females and ≤ 49 U/L for males in the rest of the world, and 2) ≤ 40 U/L for all patients (in Appendix G only). Please confirm which definitions of ALT normalisation have been used in the analyses and please provide versions of the Figures presented in Appendix N using these definitions, if they are different.

Company response: The apparent difference between the two figures is due to different definitions of ALT normalisation. The long-term extrapolation of ALT response in the overall population graph provided on 12 May was performed on aggregated IPD which used the definition of ALT normalisation as per the CSR (≤ 31 U/L for females and ≤ 41 U/L for males in Russia, and ≤ 34 U/L for females and ≤ 49 U/L for males in the rest of the world). In contrast, the histogram depicting ALT normalisation amongst the subset of virologic responder (Figure 29, Appendix N) uses the definition of ALT normalisation as per the EASL (2017) clinical practice guidelines for the management of HBV infection, namely an ALT threshold of ≤ 40 U/L.

Table 18 below represents an updated version of Figure 29 in Appendix N, using the definition of ALT normalisation as per the CSR.

Table 18: Evolution of ALT response over 48 weeks in patients showing a virologic response in the bulevirtide 2 mg treatment group (MYR 301)

Key: ALT: alanine aminotransferase; BLV: bulevirtide; ULN: upper limit of normal.
Notes: ULN: ≤ 31 U/L for females and ≤ 41 U/L for males in Russia, and ≤ 34 U/L for females and ≤ 49 U/L for males in the rest of the world. Virologic responder population represents [redacted] subjects in the bulevirtide 2 mg treatment arm.

A22. Priority question: Please provide the references from the CS as a RIS file or another file format that can be imported into EndNote.

Company response: A RIS file for references provided in the CS and clarification responses is provided in the submitted materials.

Section B: Clarification on cost-effectiveness data

Revised company base case

In light of some of the clarification questions, Gilead has revised its base case to include:

- Change of model population from the PEG-experienced sub-group from MYR 301 to the whole trial population (A5; B9);
- Change of hazard ratios (HRs) for disease progression in complete responders from 0.001 to 0 (B20);
- Change of complete responder HR from F4 to liver-related death to be equal to the HR of 0.22 for partial responders (B14);
- Inclusion of histopathology cost as part of the unit cost for livery biopsy (B39); and
- Unit cost of complete blood count has been updated to a phlebotomy cost (B40).

The new base case results are presented in Table 19 below. Total costs and QALYs and the results of sensitivity analyses are included within the appendices. All other scenarios reported within the document are applied to this base case unless stated otherwise.

Table 19: Company's revised base case cost-effectiveness results

Technologies	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
BSC	-			
Bulevirtide	[redacted]	4.82	[redacted]	£40,562

B1. Priority question. Page 126 of the CS states that, "Although the available follow-up data from MYR 301 are limited to 48 weeks, analysis of the individual patient data (IPD) indicates that response rates were still increasing at that timepoint. Therefore, the proportion of complete responders among those remaining on treatment past 48 weeks is expected to increase." The EAG had the opportunity to review the response rate figures (and underlying data) shared by the company on 12 May and concluded that biochemical response in the MYR 301 trial happened earlier than virological response. Furthermore, virological response seems to be more sustained than biochemical response, with [redacted] of patients having virological response at week 48 and less than [redacted] of patients having biochemical response at the same point in time. This is in stark contradiction with the company's argument that "ALT normalisation can be viewed as a lagging indicator of treatment response" and importantly, in contradiction with the entire model rationale, which is based on: 1) biochemical response happening later than virological response (and the former being more sustained); and 2) the definition of partial responders being virological responders only. Therefore, can the company please:

1. **Provide the clinical rationale for the observed trial data;**

Company response: It was hypothesised that treatment beyond the first 24 weeks is needed to bring about a meaningful response. As the proportion of patients achieving ALT response was lower than those achieving virologic response, ALT may be best seen as a lagging indicator. However, the EAG pointed out that the rate of ALT response appears to decline at around week 16. Upon further examination, whilst a trend in increasing response rates over time still holds true, ALT response may be better seen as an early indicator of future virologic response. This can be observed in the proportion of early ALT responders at weeks 16 and week 24 who went on to achieve a virologic response or combined response.

2. **Provide the justification for choosing a model structure in apparent contradiction to the trial data;**

Company response: In line with other hepatitides and the choice of trial endpoints, it was anticipated that biochemical response would only be achieved with sustained virologic response. Though we agree that a larger proportion of patients achieve biochemical response before virologic, this may be due to other factors that affect

ALT levels such as those discussed in A2. Furthermore, approximately [redacted]) virologic-only responders at 24 weeks went on to achieve a biochemical response at 48 weeks, indicating that ALT levels were continuing to improve in a subset of patients. Improvement in biochemical response beyond 48 weeks had to be extrapolated based on a relatively small sample size and the true proportion of patients will be known once 96-week data become available in [redacted]

3. **Explain how patients with a biochemical response only were dealt with in the economic analysis. The company's modelling approach of not capturing biochemical response alone seems to underestimate a large benefit in both treatment arms (for example, the data shared by the company shows that at 24 weeks in the bulevirtide trial arm there were [redacted] of patients with virological response and [redacted] of patients with a biochemical response).**

Company response: Biochemical response alone was not considered in the model as ALT levels (as observed in the delayed therapy arm) may improve for other reasons unrelated HDV levels, whereas a biochemical response due to HDV viral suppression requires an associated virologic response. While virological response may show some variation due to natural fluctuations in viral titre, it is an objective marker of response to treatment and thus was considered the best endpoint for an early (48 week) utility analysis.

Furthermore, the Sankey diagram in Figure *7* shows: (1) the majority of patients who achieve ALT only response at week 24 go on to achieve CR by week 48. (2) Very few ([redacted]) patients have ALT only response at week 48 therefore any benefit associated with ALT only response is expected to be minimal.

The EAG's cited response rates are incorrect: at 24 weeks; [redacted] of bulevirtide 2 mg patients had achieved a virologic response whereas only [redacted] had achieved ALT normalisation. Conversely, [redacted] of patients in the delayed treatment arm had achieved virologic response [redacted] ALT normalisation, the difference being due to only one additional patient achieving ALT normalisation.

B2. Priority question. Page 126 of the CS states that, "based on visual inspection of the pattern of observed response rates at weeks 4, 8, 16, 24 and 48, within each treatment group of MYR 301, the shape of the response rates was deemed appropriate to be fit with an EMAX function". The EAG had the opportunity to review the response rate figures (and underlying data) shared by the company on 12 May and is of the opinion that the fitted curves only provide a plausible fit to the observed data for virological response. The EAG is concerned that the curves fitted for biochemical response are a poor fit, not only for the observed period but also for the extrapolated portion of the curves. Therefore, the EAG asks that the company reconsiders the fitted curves used in the model. Furthermore, the EAG suggests that the following scenario analysis is undertaken:

1. **For the biochemical response curve in the bulevirtide 2mg group, the observed data suggests that a plateau of response is achieved at week 16 for 65% of patients and remains, on average, the same until week 48. Therefore, please include a scenario in the model where biochemical response is assumed to be 65% from week 16 until the end of the extrapolated period. For the biochemical response curve in the BSC group, the observed data does not show an obvious plateau. Therefore, please use clinical expert advice to inform when this would be expected to occur for BSC patients, and conciliate the clinical advice with the BSC trial data.**

Company response: Following the EAG's comments, a further assessment of the observed data vs the model-predicted results for the biochemical (ALT) response endpoint was performed. Two sensitivity analysis models, as described below, were further developed to address the feedback.

With the visual inspection of the data, the EMAX-based modelling was still considered appropriate to use. However, the following observations are noted:

1. There is a pattern of higher rate of response observed than predicted at weeks 16, 24 and 40, particularly compared to weeks 32 and 48 (last timepoint of available data).

2. In particular, the higher response rate at week 40, occurring between weeks 32 and 48.

While the higher response rates could be considered closer to the true underlying pattern of the data, having these intermediate timepoints with notably higher response rates does result in slightly higher predicted response rates at week 72 and 96.

In order to take a conservative approach, an initial sensitivity analysis was developed using the EMAX model for prediction excluding the observed response rate data at weeks 16, 24 and 40. In order to reduce the number of observed data exclusions, a second sensitivity analysis was developed with only the week 40 observed data excluded.

Modelling using these extrapolations was developed separately for individuals by treatment groups of “Bulevirtide 2mg” and “Delayed Treatment”. Similarly, these were separately developed for the overall study population as well as the Peg-IFN subgroup for completeness.

The graphical summary of the observed data and predicted results from the different models (1. original EMAX model, 2. the first sensitivity analysis EMAX model excluding data at weeks 16, 24 and 40, and 3. the second sensitivity analysis EMAX model excluding data at week 40.) are presented in Figure 9-Figure 12 below. Numerical results are available in excel files - ‘*ID3732_B2_Clarification_Summary_Summary_Table_ALT_Response_2_Sens.xlsx*’, ‘*ID3732_B2_Clarification_Summary_Table_ALT_Response_Peg_IFN_2_Sens.xlsx’*)

It can be seen that the predicted model results using the first sensitivity analysis model presents the most conservative estimate across all results. However, the model based on the second sensitivity analysis model also results in comparable results that have face validity.

Based on the review of these results, the first sensitivity analysis model appears to provide the best fit. Given the similarity to the submitted model and low sensitivity of results to such a minor change, a change to the economic model was not deemed necessary.

Figure 9: Observed vs. predicted ALT response from EMAX models – 2 mg bulevirtide (overall population)

Figure 10: Observed vs. predicted ALT response from EMAX models – Delayed treatment (overall population)

Figure 11: Observed vs. predicted ALT response from EMAX models – 2 mg bulevirtide (prior Peg-IFN population)

Figure 12: Observed vs. predicted ALT response from EMAX models – Delayed Treatment (prior Peg-IFN population)

B3. Priority question. Please explain the difference between the "decision tree" model structure for the first 72 weeks of the analysis, and the Markov cohort model which begins thereafter. Presently, the EAG cannot see any difference

in the model structure and in the included health states before and after 72 weeks.

Company response: The EAG is correct; from a coding standpoint the model is a Markov throughout. We simply wished to highlight the presence of stopping rules at specific timepoints, whereby cohorts of patients not achieving particular response criteria discontinue bulevirtide treatment. This required the application of conditional probabilities as per decision trees.

B4. Priority question. Please justify why 96 weeks was the chosen time point to extrapolate patients' response to, from week 48 of the trial.

Company response: Based on the EMAX extrapolations, a plateau in combined response is predicted soon after 96 weeks (predicted response rate increased by only 3% between week 72 and 96). This was therefore felt to be an appropriate period at which to apply a final stopping rule that ensures that patients failing to achieve sufficient response are not kept on bulevirtide for longer than is necessary. Furthermore, patients from the MYR 301 study continue to be followed up and data from up to 96 weeks of treatment are anticipated to become available in [redacted].

B5. Priority question. Please justify why 72 weeks was the chosen time point to decide when patients are deemed either complete responders or non-responders.

Company response: To clarify, in the model, non-responders are identified at week 48 based on the achievement of virological response, at which point they are assumed to discontinue treatment. This leaves only partial responders (patients achieving virological response only) and complete responders (patients achieving both virological and biochemical response) on bulevirtide. Based on the EMAX extrapolation models, complete response was only predicted to increase by 3% between weeks 72 and 96, thus it was felt that 72 weeks was a reasonable compromise between further improvement in response and ongoing cost.

Furthermore, the timing of the stopping rule has little impact on the ICER:

- Changing it from 72 to 96 weeks increases it from £40,562 to £40,620
- Changing it from 72 to 48 weeks increases it from £40,562 to £41,231

B6. Priority question. Please include a scenario analysis in the model (through the use of a user-selectable dropdown menu) which aggregates the F2 and F3 states, i.e. not only assuming that patient distribution at baseline is between the F3 or F4 states, but assuming that patients regressing from F4 cannot go below the same F3 aggregated moderate/severe fibrosis state.

Company response: This scenario has been added into the model and the user-selectable drop-down is in cell K64 of the 'SETTINGS' sheet. The results for this scenario are reported in the table below.

Table 20: Cost-effectiveness results for requested scenario B6

Technologies	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	Base-case ICER
BSC					
Bulevirtide	[redacted]	4.97	[redacted]	£38,535	£40,562

It can be seen that the combined effect of aggregating the F2 and F3 health states and removing the possibility of any disease regression below F3 reduces the ICER by approximately £2,000 per QALY.

Treatment effectiveness

B7. Priority question. The calculations included in the model tab "DT_Calculations" to estimate the transition probabilities in the model lack clarity. Please provide a detailed explanation of the assumptions and the calculations made to obtain the transition probabilities between non-responders; partial responders; and complete responders in the model.

Company response: The '*DT_Calculations*' model tab estimates the decision tree element of the model. It determines the proportion of patients who transition between non-responders; partial responders; and complete responders. We have assumed the following transitions are possible:

- Non-Responder → Partial Responder
- Non-Responder → Complete Responder
- Partial Responder → Complete Responder

The backward transitions of the above are assumed to not take place (negative values) using a maximum function. The steps in the calculation of proportions for the above 3 transitions are described below:

i. First, the proportion of patients transitioning from non-responder to partial or complete responder is calculated as the percentage increase in partial or complete responders at each cycle (J12:J15). Partial or complete responders are computed as the sum of complete and partial responders.

ii. The proportion of patients transitioning from non-responder to complete responder (L12:L15) is calculated as:

    - The percentage increase of complete responders among partial and complete responders, if the percentage of complete responders among partial/complete responders is **increasing.**

    - The proportion of complete responders, if the percentage of complete responders among partial/complete responders is **decreasing**.

iii. The proportion of patients transitioning from non-responder to partial responder is calculated as the difference between (i) and (ii).

iv. The proportion of patients transitioning from partial responder to complete responder (M12:L15) is calculated as:
    - If the percentage of complete responders among partial/complete responders is **increasing**, the percentage increase of complete responders among partial and complete responders.
    - If the percentage of complete responders among partial/complete responders is **decreasing**, the percentage increase of complete responders.

v. Finally, maximum functions are used to avoid negative values or backward transitions.

B8. Priority question. The EAG's understanding is that transition probabilities for the first 2 cycles of the model were estimated based on some assumptions,

and did not use the raw IPD data from the trial (for example, the data shared by the company shows that at 24 weeks in the trial there were 50% of patients with virological response and 60% of patients with a biochemical response, which is not the case in the model). Therefore, please use the IPD available from MYR 301 to estimate the transition probabilities between non-responders; partial responders; and complete responders in week 24 and week 48 in the base case model. Alternatively, please include a scenario analysis (through the use of a user-selectable dropdown menu) where these transition probabilities are included.

Company response: The IPD provided to the EAG details the total number of patients who received any response within the category described i.e. the virologic responders are inclusive of those with complete response. Partial responders in the model are those with virologic response only. This was calculated by subtracting the % of complete responders from the % of virologic responders, leaving biochemical-only and complete non-responders allocated as non-responders in the model. The patient numbers used for these calculations can all be found in the BG_CLINICAL sheet of the model.

In the PEG-IFN experienced subpopulation, at 24 and 48 weeks of treatment, only [redacted] and [redacted] patients had complete (combined endpoint) response out of the 55 patients summed across both the 2 mg bulevirtide and delayed treatment arms, respectively. [redacted] and [redacted] patients had partial (i.e., virologic only) response out of the 55 patients, and [redacted] and [redacted] patients had non-response out of the 55 patients, respectively. Creating transition matrices for such small patient numbers can lead to highly unstable transitions when extrapolated, hence we preferred to use the proportions in each response category directly and use a regression to predict future proportions. The same is applicable to the overall trial population, which only has 49-51 patients in each arm, with small numbers of transitions leading to potentially large transition probabilities.

Furthermore, in order to be leveraged within the economic model structure, these data would need to be further stratified by the initial starting health state (i.e., degree of fibrosis/compensated cirrhosis) which would further reduce the sample size from which to map these data onto health state transitions in the model. Therefore, we do

not believe they would constitute robust estimates for use in estimating health state transitions. In contrast, the values for the natural history used in the model come from studies examining considerably larger numbers of patients, and thus can better reflect the transitions that would be expected within the 24 to 48 week time frame, particularly for best supportive care patients.

B9. Priority question. Please include a scenario analysis (through the use of a user-selectable dropdown menu) using the full trial population clinical effectiveness data. More specifically, please use the response; partial response; and no response data for the full trial population to estimate the transition probabilities in both arms of the model (please take into consideration the points raised in question B1 and B2).

Company response: This scenario is already available through the use of a user-selectable dropdown in the original submitted model. The drop-down is located in cells F8:G8 of sheet 'CLINICAL' in the model. In light of our response to clarification question A5 we have now updated our base-case to reflect the overall trial population. The results for this new base-case are reported in Table 19. All base-case and sensitivity analyses results are also reported separately in the appendix document submitted alongside these clarification responses.

B10. Priority question. Please include a scenario analysis (through the use of a user-selectable dropdown menu) using the data requested in question A8 to estimate two sets of transition probabilities between non-responders; partial responders; and complete responders, separately, for patients with and without cirrhosis at baseline.

Company response: We believe that this scenario is not feasible, for reasons outlined in the response to question B8.

B11. Priority question. Please explain why the discontinuation rate seen at the end of 48 weeks (2.04%) was assumed to be constant for the remainder of the model timeframe. Please provide a scenario analysis where this rate is

increased over time to assess the impact of this assumption on the cost-effectiveness results.

Company response: There are currently no long-term data on adherence for bulevirtide. Furthermore, there are no other effective treatments for hepatitis delta. It is therefore expected that patients responding to therapy are likely to continue using treatment, which was why the discontinuation rate at the end of 48 weeks [redacted] was assumed to be constant for the remainder of the model timeframe. The discontinuation rate impacts both effectiveness and the cost of bulevirtide treatment. We have included the ability to increase the discontinuation rate over time in the model adjacent to the existing discontinuation rates in the model. This is currently set to 0%.

B12. Priority question. Please provide a comparison between the trial outcomes at week 48 and the predicted model outcomes by filling the table below.

Table 21: Comparison of MYR 301 vs model fibrosis progression

	MYR 301		Model	
From baseline	BSC	BLV 2 mg	BSC	BLV 2 mg
METAVIR fibrosis stage improvement	[redacted]	[redacted]	[redacted]	[redacted]
METAVIR fibrosis no change	[redacted]	[redacted]	[redacted]	[redacted]
METAVIR fibrosis stage worsening	[redacted]	[redacted]	[redacted]	[redacted]

Company response:

This analysis was carried out by:

- Selecting the following revised base case settings:
    - Overall population
    - HR for Liver-Related Death to 0.22 (the value applied to Partial Responders)
    - 0 for other HRs (i.e. no progression)
- Setting all progression to HCC or LT to zero (to capture only progression to fibrosis/cirrhosis health states).
- Dividing the state occupancy by the % alive.
- Setting the model baseline characteristics to 100% for each of F2, F3 and F4 in turn and recording the proportions who had improved, worsened or not changed health state by week 48.
- Reweighting the results by the proportion of patients in each health state at baseline.

Complete responders

B13. Priority question. Compared to non-responders, responders have a lower (close to 0) probability of progressing from the F3 to F4 states in the model, as well as progressing from the F4 state to a decompensated cirrhosis state. However, it is possible that the benefits associated with being a responder are being overestimated in the model, given the company's assumption that being a responder vs a non-responder in the F0-F4 states is also associated with a lower probability of HCC. Therefore, please:

1. **Justify the clinical rationale for this assumption.**

Company response: The meta-analysis did not differentiate between patients with non-cirrhotic vs. compensated cirrhotic disease in terms of their transition to HCC if they were HDV RNA+ vs. RNA-, and thus to ensure a reduction commensurate with that observed from the meta-analysis for patients responding to treatment it was

assumed that responders in any F-stage would experience a slower progression to HCC. Furthermore, we do not believe that this would have a significant impact on model results given that the HR from F4 to HCC was not amongst the 10 most impactful parameters within the tornado diagram (Figure 20 of the CS).

2. **Include a scenario analysis in the model (through the use of a user-selectable dropdown menu) where the impact of being a responder in the F0-F4 states on HCC is removed from the model (and only the relationship between being in each individual F-state and developing HCC is maintained in the model).**

Company response: The scenario to examine the impact of removing slowed disease progression to HCC from the F-stage health states can currently be performed by setting the user-modifiable HR fields for the F0-2→HCC, F3→HCC, and F4→HCC values to 1. This can be done via cells I84, I85 and I87 in the 'INPUTS' sheet respectively. The results for this scenario are reported below.

Table 22: Cost-effectiveness results for requested scenario B13.2

Technologies	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	Base case ICER
BSC	-				
Bulevirtide	[redacted]	2.71	[redacted]	£51,565	£40,562

B14. Priority question. Please clarify if the HR of 0.001 for responders (vs non-responders) used in the model to estimate mortality in the F4 state is a mistake, and should instead be 1 as is the case with responders in the decompensated cirrhosis; HCC; and liver transplant states. If this is a mistake, please correct the model and present updated deterministic and probabilistic results. If this is not a mistake, please provide a clinical rationale for this assumption, given that the CS states that excess mortality was only modelled in association with severe liver disease (and not response status).

Company response: The statement in the company submission was incorrect. A HR of 0.22 is also applied to the excess risk of liver-related death in the F4 (CC) state for partial responders which logically should be increased for complete responders. However, we agree with the ERG that to assume no liver-related excess

mortality lacks face validity, so we have replaced 0.001 with the HR of partial responders of 0.22 from the meta-analysis in our updated base case.

Partial responders

B15. Priority question. The studies included in the meta-analysis conducted by the company do not seem to restrict response to virological response (i.e. partial response). Therefore, it is likely that a proportion of patients in the study with virological response also had biochemical response. Therefore, the HRs obtained in the company's meta-analysis are likely to overestimate the effect of being a partial responder vs a non-responder in the model. Therefore, can the company please:

1. **Confirm that the studies included in the meta-analysis did not exclude biochemical responders;**

Company response: We can confirm that the studies in the meta-analysis did not focus on patients with virologic response only, however the studies could be inclusive of patients experiencing a biochemical response concurrently.

2. **Justify the company's approach and discuss the possibility that the HRs used are overestimating the benefit associated with partial response:**

Company response: To inform the relationship between the composite response endpoint and disease progression, a modified Delphi panel approach was undertaken. Three different conceptual approaches were discussed with an international panel (members from US, Europe and Turkey) of 11 clinicians experienced in treating HDV infection. The three approaches were: (1) assuming the 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 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 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 analog approach. Rationale for

choosing the Approach 1 approach 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. As the generally accepted definition of consensus in a Delphi panel is achieving agreement greater than 75%, and since we reached 82% agreement, consensus was considered to be achieved for this topic.

Following this, an SLR and meta-analysis was carried out to produce the HRs used in the economic model, which the EAG has been provided. While the studies included in the meta-analysis did not exclude those who may have also achieved ALT normalisation (i.e., corresponding to virologic response only), notably there were substantial improvements in ALT levels across all patients with virologic response, including those without achieving the combined endpoint response. In the post-hoc analysis of change of ALT levels, the evolution of the ALT response over the 48 weeks of data amongst virologic responders and non-responders in the bulevirtide 2 mg treatment arm appears to show a greater proportion of patients achieving either ALT normalisation or improvement in ALT response as compared to subjects in the delayed treatment group. Thus, while not achieving the full normalisation of ALT levels, patients even with virologic response only appear to experience a substantial improvement in liver biochemistry which we believe may confer benefits similar to a full ALT normalisation response.

Figure 29: Evolution of ALT response over 48 weeks in patients showing a virologic response in the bulevirtide 2 mg treatment group (MYR 301)

Key: ALT: alanine aminotransferase; BLV: bulevirtide; ULN: upper limit of normal.
Notes: ULN = 40 IU/L. Virologic responder population represents [redacted] in the bulevirtide 2 mg treatment arm.
Source: Data on file (7)

Figure 30: Evolution of ALT response over 48 weeks in patients showing a non-virologic response in the bulevirtide 2 mg treatment group (MYR 301)

Key: ALT: alanine aminotransferase; BLV: bulevirtide; ULN: upper limit of normal.

Notes: Notes: ULN = 40 IU/L. Virologic non-responder population represents 14 of 49 subjects in the bulevirtide 2 mg treatment arm.
Source: Data on file (7)

Figure: Evolution of ALT response over 48 weeks in the delayed treatment arm (MYR 301)

Key: ALT: alanine aminotransferase; BLV: bulevirtide; ULN: upper limit of normal.
Notes: ULN = 40 IU/L
Source: Date on file (7)

3. **Include a scenario analysis in the model (through the use of a dropdown menu) where the HRs are adjusted to reflect clinical expert opinion (or other relevant sources) to account for the benefit associated with partial responders vs non-responders.**

Company response: Unfortunately, we are unable to provide this scenario as we have not been able to engage with clinical experts during the short time frame between receiving the clarification questions and the response deadline. However, as discussed in part 2, the approach for linking response to impact on progression was validated by a panel of clinical experts in a Delphi panel.

B16. Priority question. The EAG could not find the 2.39 HR in the company's meta-analysis, used in the model to estimate the risk of partial responders vs

no-responders progressing in their fibrosis stage (and reported to have been taken from the company's meta-analysis). Please clarify where the HR can be found and how it was calculated.

Company response: The HR of 2.39 was sourced from Figure 42 in the report (shown below), which focused on the meta-analysis only of studies for the any liver disease event endpoint for HDV RNA positive vs. negative patients.

Figure 13: Copy of figure 42 from company meta-analysis

B17. Priority question. The EAG could not find the 4.58 HR in the company's meta-analysis, used in the model to estimate the risk of responders vs no-responders dying from the compensated cirrhosis state (and reported to have been taken from the company's meta-analysis). Please clarify where the HR can be found and how it was calculated.

Company response: The HR of 4.58 was sourced from Figure 51 in the report (shown below), which focused on the meta-analysis only of studies for the any liver disease event endpoint for HDV RNA positive vs. negative patients.

Figure 14: Copy of figure 51 from company meta-analysis

B18. Priority question. Please explain why the HR for responders vs partial responders for liver transplant estimated in the meta-analysis was not used in the economic analysis.

Company response: Patients can only move to LT from the DCC or HCC health states. Given that patients are assumed to discontinue therapy upon reaching the DCC / HCC health states, further reduction in progression to LT from these health states was not directly included in the model.

Furthermore, the estimates for the impact of HDV RNA negativity vs. positivity on rate of liver transplant was based on studies looking at patients who may be in earlier stages of liver disease (i.e., in F0-F4). Given that patients would first progress from F0-F4 to DCC or HCC prior to LT, and that we assume treatment-related reduction in progression from F0-F4 to DCC and HCC, we assumed that adding in additional reduction from DCC to HCC to LT would potentially double count the benefits of treatment, and thus not including this reduction directly in the model would be a more conservative approach.

B19. Priority question. The HRs from the meta-analysis were varied by +/- 20% in PSA. However, the 95% confidence intervals were available from the meta-

analysis conducted by the company. Therefore, please replace the confidence intervals used in the PSA by the ones provided by the meta-analysis.

Company response: The model has been updated to include the 95% confidence intervals for the HRs from the meta-analysis in the PSA instead of +/- 20%.

B20. Please explain why complete responders have a HR of 0.001 vs no responders for disease progression, instead of a HR of 0 (or alternatively, a per-cycle probability of 0%) given the clinical rationale that complete responders have no disease progression.

Company response: HRs of 0 are not a clinical reality, hence why we felt that the use of 0.001 was more appropriate. However, we agree with the EAG that 0 could instead be implemented and we have changed the values accordingly in our updated model.

Natural history of disease

B21. Priority question. The CS lacks clarity around how the estimates used to model natural history of disease were sourced and calculated. The EAG also believes that the reference (and study included in the submission pack) given by the company for the Dakin H et al., 2010 paper (Dakin H, Fidler C, Harper C. Mixed treatment comparison meta-analysis evaluating the relative efficacy of nucleos(t)ides for treatment of nucleos(t)ide-naive patients with chronic hepatitis B) for most estimates is incorrect, and should instead be the Dakin H *et al*., 2010 - Cost–Utility Analysis of Tenofovir Disoproxil Fumarate in the Treatment of Chronic Hepatitis B. Therefore, can the company please:

1. **Provide the correct Dakin H *et al*., 2010 study, particularly the appendix 1 referenced in the study which contains all the transition probabilities used;**
2. **Respond to the requests for clarification included in the table below.**

Company response: Please see Table 23 below for the requested information.

Table 23: Detailed sources for transition probabilities applied in the model

Health State		Annual Transition Probability		Clarification
From	**To**	**Base Case**	**Request for clarification**	
F3	HCC	2.86%	Please provide the calculations used to obtain the "scaled relationship of F4-->HCC based on the relationship in HCV from Dienstag et al., 2011", together with the estimate used from Dienstag et al., 2011.	• Dienstag et al., 2011(14) reported that clinical outcomes occurred at a rate of 7.5% per year in patients with cirrhosis as compared to 3.3% per year in patients with advanced fibrosis; this ratio was multiplied by the base rate of 2.3% F4→HCC transition per year and scaled by the increase risk of HCC from Alfaiate et al., 2020 (15) (2.77 higher risk for HDV infection vs. HBV monoinfection).
F3	F4	15.07%	Please provide the estimate used from the Papatheodoris GV *et al*., 2008 study.	• Rationale was sourced from Bermingham et al., 2016 (16), a modelling study in HBV patients; please find the rationale from this study noted below: • As reported in a review by Fattovich 2003 (17), the incidence of cirrhosis in people with predominantly HBeAg positive CHB ranges from 2 to 5.4 per 100 person years with a cumulative incidence of 8% to 20% over a five year period. As in the study by Dakin et al, 2010 (18), the upper limit of this estimate was used to inform this value. This is equal to an annual probability of 5.3% and a 95% confidence interval of 2.3% to 11.8%. This estimate is slightly greater than the one used by Wong 2011 (19) (mean 4.4%, 95% CI 2.2% to 8.8%) which was informed by Liaw

				1987 (20), and Veenstra 2007 (21). The GDG agreed that the value from Dakin 2010(12) more closely matched their expectation of this transition in a UK population. • Da et al., 2019 (22) reported a 2-3x fold relative risk increase in the occurrence of cirrhosis in HDV vs. HBV monoinfection. • Therefore, the annual probability of 5.3% was scaled by 3x.
CC (F4)	DC	10.67%	Please specify the source and the estimate used from the Dakin H *et al*., 2010 and justify the choice of this parameter.	• Rationale was sourced from Bermingham et al., 2016, (23), a modelling study in HBV patients; please find the rationale from this study noted below: • Data used to inform this transition probability was obtained from Dakin 2010 (18) and is similar to that used by Wong 1995(19) of 5.9% (range 3.8% to 9.5%), attributed to Fattovich 1995 (24). According to this study, neither the presence of HBV DNA nor HBeAg predicted the development of decompensation. Therefore, the same probability was applied to people with HBV DNA negative CC and HBeAg negative CHB. • The annual transition probability of 5.0% is then increased to represent faster progression in HDV patients using the 2.0 HR estimated from Fattovich et al., 2000 (25).
	HCC	6.24%	Please specify the source and the estimate used from the Dakin H *et al*., 2010 and justify the choice of this parameter.	• Rationale was sourced from Bermingham et al., 2016 (23), a modelling study in HBV patients; please find the rationale from this study noted below:

				• Among people with CHB and cirrhosis, the annual probability of developing HCC ranges from 0.2% to 7.8%. The REVEAL study trial (26) found that compared to people with HBV DNA of less than 300c/ml, the hazard ratio (HR) of developing HCC was 21.8 (95% CI 14.9 to 32.0) for people with liver cirrhosis. This transition probability was calculated by multiplying this HR by the annual rate of HCC from Undetectable HBV DNA (transition 14). The resulting value is similar to the value used by Dakin 2010 and Wong 1995 (mean 2.4%, 95% CI 0.0% to 8.0%). According to the systematic review and meta-analysis by Singal 2011(26), the probability of developing HCC is the same for people with HBV DNA positive compensated cirrhosis (CC) as for those with HBV DNA negative CC. This is the same assumption made by Dakin 2010. • This 2.3% transition per year was scaled by the increase risk of HCC from Alfaiate et al., 2020 (2.77 higher risk for HDV infection vs. HBV monoinfection).
	Liver-Related Death	7.26%	Please provide the estimate used from the Fattovich G *et al.*, 2003 study.	• Based on the value used in Bermingham et al., 2016 (3.7%), which is sourced from Fattovich et al., 2003 (17): In the EUROHEP cohort of 161 untreated patients with HBsAg positive, HDV negative compensated cirrhosis the 5-year probability of survival was 86% and the incidence per 100 person years of liver related death was 3.5; this value is similar to the 3.7% used in the Bermingham et al., 2016 model.

				• This value was increase by 2-fold as per Fattovich et al., 2000.
DCC	HCC	7.83%	Please specify the source and the estimate used from the Dakin H *et al*., 2010 and justify the choice of this parameter.	• Rationale was sourced from Bermingham et al., 2016 (23), a modelling study in HBV patients; please find the rationale from this study noted below: • A recent systematic review of the incidence of HCC in CHB found that in 12 studies HCC was diagnosed in 78 of 779 people with compensated and 18 of 148 people with decompensated cirrhosis. The resulting odds ratio (OR 1.24, 95% CI 0.72 to 2.15) was multiplied by the probability of HCC from CC (transition 16) using probabilistic simulation. Note that this calculation is in contrast to finding by Singal 2011 and the assumption by Dakin 2010 and Wong 1995 that people with DC have the same probability of developing HCC as people with CC. This 2.9% transition per year was scaled by the increase risk of HCC from Alfaiate et al., 2020 (2.77 higher risk for HDV infection vs. HBV monoinfection).
	LT	1.55%	Please specify the source and the estimate used from the Dakin H *et al*., 2010 and justify the choice of this parameter.	• Rationale was sourced from Bermingham et al., 2016 (23), a modelling study in HBV patients; please find the rationale from this study noted below: • According to Dakin 2010, data from the UK National Transplant Database (27) suggests that approximately 25 liver transplants are conducted in the UK every year for CHB. If the total prevalence of CHB in the UK is 0.3% and 65% of people with CHB are diagnosed,

				there are around 115, 500 people in the UK with diagnosed CHB, of whom around 1600 (1.4%) would have HCC or DC and be indicated for transplant (42). Therefore the annual probability of a patient with DC or HCC undergoing liver transplant is 1.55%. The minimum range assumes no liver transplants are conducted for DC and the maximum is an upper estimate from the GDG.
HCC	LT	1.55%	Please specify the source and the estimate used from the Dakin H *et al*., 2010 and justify the choice of this parameter.	• Rationale was sourced from Bermingham et al., 2016 (23), a modelling study in HBV patients; please find the rationale from this study noted below: • This figure was based on the assumption by Dakin 2010 that the risk of liver transplant from HCC is equal to that from DC; the minimum value assumes that no liver transplants are conducted for HCC and the maximum was assumed to be twice the mean value.
	Liver-Related Death	56.00%	Please specify the source and the estimate used from the Dakin H *et al*., 2010 and justify the choice of this parameter.	• Value has been used in Bermingham et al., 2016 and Veenstra et al., 2007 economic evaluations of HBV treatments.
LT	Liver-Related Death	21.00%	Please specify the source and the estimate used from the Dakin H *et al*., 2010 and justify the choice of this parameter.	• Value has been used in Bermingham et al., 2016 and Veenstra et al., 2007 (21) economic evaluations of HBV treatments, sourced from Bennett et al., 1997 (28)
Post-LT	Liver-Related Death	5.70%	Please specify the source and the estimate used from the Dakin H *et al*., 2010 and justify the choice of this parameter.	As above.

B22. Priority question. The EAG is concerned that survival is overestimated in the model. For example, the proportion of responders and non-responders alive at 5 years in the model in the bulevirtide arm is 99% and 80%, respectively, which compares to the estimates in the Fattovich G *et al.*, 2003 study of survival without; and survival after decompensation of 86% and 28%, respectively. Given that Fattovich G *et al.*, 2003 reports survival for hepatitis B (which the company has assumed is higher than survival in hepatitis D by 2-fold), this suggests an overestimation of survival in the model. Therefore, please consider using KM data available in literature (from Fattovich G *et al.*, 2003, or another suitable source) to estimate long-term survival in the model, instead of using a constant annual probability of liver-related death from the CC;DCC; HCC; and LT states. Please consider fitting survival curves to KM data and extrapolating these in order to more accurately capture long-term survival, following the guidance in the NICE Decision Support Unit TSD 19.

Company response: In the model base case, approximately 40.22% of patients have non-cirrhotic (F2-F3) disease at baseline, while 59.78% of patients would have compensated cirrhosis at baseline. The estimates noted above by the EAG focus on survival in DCC patients, which only a subset of these patients would reach during the 5-year time horizon noted above. We believe that survival of HDV patients is appropriately modelled given the Fattovich (17) study for the following reasons:

- The Fattovich study provides estimates of long-term survival in non-cirrhotic and compensated cirrhotic patients:
    - "In long-term studies of untreated patients with chronic hepatitis B, both HBeAg positive and HbeAg negative, without preexisting cirrhosis at baseline and without HDV infection, the incidence of liver related death was low and ranged from 0 to 1.06 per 100 person years (personal communication of the authors of refs. [25, 26, 51, 64])."
    - Furthermore, in CC patients from the Fattovich study, the probability of survival is approximately 80–86% at 5 years in patients with compensated cirrhosis.
- Using these estimates, the predicted survival for BSC (i.e., non-responder) patients was estimated based on the starting population in the model:

- Assuming a 2x higher rate of death in non-cirrhotic patients per Fattovich et al., 2000, and a 1.06% annual incidence of mortality in these patients, the estimated 5-year mortality rate in non-cirrhotic (i.e., F2-F3) patients would be 10.11% (i.e., 89.89% of patients alive).
- Assuming 2x higher rate of death in compensated cirrhotic patients per Fattovich et al., 2000, and assuming 80%-86% of F4 HBV patients would be alive at 5-years as per Fattovich et al., 2003, the estimated 5-year mortality rate in F4 patients would be 26-36% (i.e., 64-74% of patients alive).
- Based on a weighted average of the non-cirrhotic and cirrhotic patients, this would yield an estimate of 74%-80% survival at 5-years, in line with the current prediction for non-responders in the model.

B23. Priority question. Please consider using KM data and survival analysis to estimate the long-term probability of other disease events in the model. For example:

1. **The company assumes a constant annual probability of death for HCC patients of 56%; however, the Bolondi *et al*. 2001 study provides KM data indicating that mortality for HCC patients is 30%; 40%; 50%; and 60% at years 1, 2, 3, and 4, respectively. Using KM data, with respectively fitted and extrapolated survival curves, would have more accurately estimated the probability of events.**
2. **The company assumes a constant annual probability of decompensation of 10.67%; however, the Fattovich G *et al.* 2003 study provides KM data on time to decompensation showing that approximately 5%; 10%; 13%; 15%; and 30% of patients have decompensated at years 1; 2; 3; 5; and 10. Using KM data, with respectively fitted and extrapolated survival curves would have more accurately estimated the probability of events.**
3. **If the company decides to not use survival analysis, please consider running a scenario analysis where the different annual probabilities of events are used in the model, as per the data**

referenced by the EAG in these sources, instead of assuming constant rates.

Company response: We digitised and used an exponential curve fit to the alternatives for HCC mortality (Bolondi et al. 2001) and decompensation (Fattovich et al. 2003). These are included as a scenario in cell H21 of the 'Natural History' inputs tab in the model. The results for this scenario are reported in Table 24.

Table 24: Cost-effectiveness results for scenario where alternative transition probabilities applied to model disease natural history

Technologies	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	Base-case ICER
BSC					
Bulevirtide	[redacted]	4.54	[redacted]	£43,493	£40,562

In order to use time-dependent transition probabilities in the model, the model would need to be structurally changed to implement tunnel states as we would need to know when patients entered each state. The use of an exponential curve fitted to the Bolondi et al. (2001) and Fattovich et al. (2003) data is a reasonable and informative solution and suggests the impact on the ICER may be relatively limited.

B24.Priority question. Farci *et al.* 2004, used by the company to estimate the probability of fibrosis regression, reported that 4 out of 6 patients who had active cirrhosis in the first 3 liver biopsies showed an absence of fibrosis in the last liver biopsy, after a mean of 11.5 years following completion of therapy (with IFN-alfa). Treatment lasted 48 weeks in the study, and the initial 3 liver biopsies occurred: before enrolment; at the end of treatment; and at 6 months after the completion of therapy, respectively. Therefore, fibrosis regression did not start occurring until at least 72 weeks after treatment initiation. However, the company has assumed that fibrosis regression starts occurring within the first 24 weeks of treatment (i.e. first model cycle). Please adjust this in the model (or conduct a scenario analysis) where fibrosis regression only starts occurring from cycle 4 onwards (i.e. 96 weeks) in the model.

Company response: The model has been updated to include a scenario where fibrosis regression starts occurring from cycle 4 onwards (i.e., 96 weeks) in the model (SETTINGS sheet cell P58). Data from the MYR 301 trial suggest that

patients may experience regression even within the first 48 weeks of the trial, that is, whilst on treatment (see Table 21). The impact on the ICER is negligible.

Table 25: Cost-effectiveness results for requested scenario B24

Technologies	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	Base case ICER
BSC	-				
Bulevirtide	[redacted]	4.78	[redacted]	£40,901	£40,562

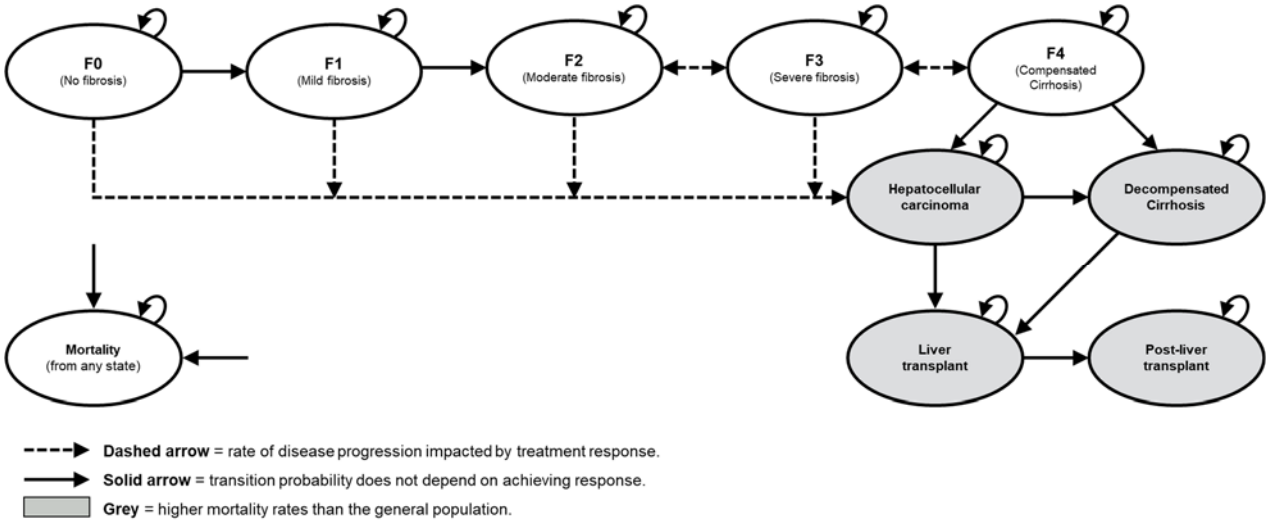
B25. Priority question. Please consider using the 95% confidence intervals in the relevant studies used to source HRs for disease progression to run the PSA in the model, rather than varying mean estimates by +/- 20% in PSA.

Company response: Model has the updated to use the 95% confidence intervals for HRs for disease progression to run the PSA in the model.

B26. Please clarify if the model structure reported in Figure 17 is incorrect in representing that only patients with HCC can progress to LT, given that the model also allows DC patients to move to LT.

Company response: The corrected model structure diagram is provided in Figure 15.

Figure 15: Economic model structure



Mortality

B27. Priority question. Please provide the clinical rationale behind liver-related death in the CC state being higher for hep D patients vs hep B patients, while liver-related death associated with DCC; HCC; and LT being assumed to be the same for hep D and hep B patients.

Company response: In Gheorge et al., 2005 (29), HDV patients had 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. For a cohort of patients with 100% compensated cirrhosis (i.e., 100% F4) entering the model, the probability of survival at 48, 96, and 264 weeks were projected at 92.4%, 78.1%, and 51.6%, respectively. Given that the model results were generally in line with survival observed in the literature, no further adjustment to liver-related mortality for more advanced health states was added. Furthermore, in discussions with clinical experts, they did not believe that the risk of liver-related death would be higher for HDV vs. HBV mono-infection after patients had progressed to liver cancer / HCC, liver decompensation, or liver transplant.

B28. Priority question. Please explain why it was assumed that patients in the F2 and, especially, F3 states have the same mortality as the general population (regardless of response status). This assumption is clinically implausible as all patients in the model have hepatitis B (thus should experience an increased mortality). Please adjust the mortality of these patients to, at least, reflect the underlying hepatitis B (please see question B22).

Company response: In prior models of HBV patients with non-cirrhotic disease (including those with F2 and F3 disease), the rates of excess mortality either have been low or not considered (i.e., only general population level mortality applied). In TA173 in the model for tenofovir disoproxil fumarate, patients with viral suppression were assumed to have a rate of excess mortality associated with viral suppression ~0.35%. In TA153, only transitions to liver-related mortality were considered from DCC or HCC, with excess mortality due to liver disease not considered for patients with compensated cirrhosis (F4) nor patients with decompensated liver disease. Furthermore, a more recent modelling study (Bermingham et al., 2016) did not

consider excess mortality due to liver disease in patients with non-cirrhotic disease. Furthermore, in our discussions with clinical experts, these experts did not believe there would be excess mortality related to HDV nor HBV for patients without liver cirrhosis.

B29. Please confirm that the statement on page 134 of the CS which states that excess mortality is only applied for the post liver-transplant state is incorrect.

Company response: This was a typographic error and should have read "from the CC state onwards". Excess mortality is applied to the following health states: compensated cirrhosis (CC), decompensated cirrhosis (DCC), hepatocellular carcinoma (HCC), liver transplant (LT), post liver transplant (PLT).

Quality of life

B30. Priority question: The EAG would like to understand the methodology used in the Gilead Data on File - MYR 301 W48 analysis_EQ-5D analysis report further and how it relates to the data presented in Table 52 of the CS. More specifically:

1. **Please confirm if all the utility analyses in the Data on File document are based on the full trial population of MYR 301 or the IFN pre-treated subgroup were used.**
   Company response: This analysis was based on the full trial population.

2. **Please confirm if all the regression analyses in the Data on File document including treatment as independent variables only included the BSC and the bulevirtide 2mg arms from the trial (and did not include bulevirtide 10mg).**
   Company response: We can confirm this is correct. All regression analyses only included the DT and bulevirtide 2 mg arms from the trial.

3. **Please provide the outcomes of the stepwise approach used to assess the statistical significance of each independent variable of models 1, 2,**

and 3, and provide the final Tobit model used (together with the p-values associated with each variable) to obtain the coefficients reported in Table 52.

Company response: We did not perform a stepwise approach. Based on internal discussion and expert opinion, we considered liver cirrhosis status at baseline and responder status at week 48 as the predictors in the model. Please find below the R code used to generate the results for the Tobit model.

```
data = data %>%
                    filter(ARMCD!="C")%>%
                    select(liver_cirrhosis, composite,EQ_8,EQ_1)

data = data[complete.cases(data),]
data = data %>% distinct()

x = cbind("Baseline eq5d" = data$EQ_1,"liverCir" = as.factor(data$liver_cirrhosis),
"composite" = as.factor(data$composite))

data$d = rep(1,nrow(data))
m2 <- crq(Curv(EQ_8, d, "right") ~ x, tau=0.5, method="Powell", data=data)
summary(m2)
```

4. **Please discuss if pre-treatment with IFN-alfa was found to be a statistically significant predictor of utility in the final Tobit model.**

   Company response: Pre-treatment with IFN-alfa was not found to be a statistically significant predictor of utility as the p-value (0.640) is greater than the fixed level of significance (0.05) in the Tobit model (as shown in Table 26 below).

Table 26*:* Regression output from final Tobit model of MYR 301 EQ-5D analysis, including pre-treatment with IFN-alfa

	Estimate	(95% CI)	p-value
(Intercept)	[redacted]	[redacted]	[redacted]
xBaseline eq5d	[redacted]	[redacted]	[redacted]
xliverCir	[redacted]	[redacted]	[redacted]
xcomposite	[redacted]	[redacted]	[redacted]
xPREIFNT	[redacted]	[redacted]	[redacted]

5. **Please discuss if response status and METAVIR fibrosis stages were both included in the final Tobit model and if these were both found to be statistically significant predictors of utility in the final Tobit model.**
   Company response: Neither response status nor METAVIR fibrosis stages were found to be statistically significant predictors of utility as the p-values is greater than the fixed level of significance (0.05) in the final Tobit model.

Table 27: Regression output from final Tobit model of MYR 301 EQ-5D analysis, including response status and METAVIR fibrosis stages

	Estimate	(95% CI)	p-value
Intercept)	[redacted]	[redacted]	[redacted]
xBaseline eq5d	[redacted]	[redacted]	[redacted]
xliverCir	[redacted]	[redacted]	[redacted]
xcomposite	[redacted]	[redacted]	[redacted]
xF0_F1	[redacted]	[redacted]	[redacted]
xF2	[redacted]	[redacted]	[redacted]
xF3	[redacted]	[redacted]	[redacted]
xF4	[redacted]	[redacted]	[redacted]

6. **Please discuss if cirrhosis at baseline was found to be a statistically significant predictor of utility in the final Tobit model.**
   Company response: Cirrhosis at baseline was not found to be a statistically significant predictor of utility in the final Tobit model as the p-value was greater than the level of significance (0.05).

7. **Please explain the differences between the coefficients reported in Table 52 of the CS for the Tobit regression and the data presented in Table 3c.**
   Company response: The coefficients reported in Table 52 are correct. Unfortunately, the supporting document submitted is an older version. We have submitted the updated document alongside our clarification responses in which the relevant table is Table 3a.

8. **Please provide the utility value for non-responders estimated with the final Tobit model used by the company to estimate the utility increment for responders vs non-responders ([redacted]).**

Company response: The utility increment was derived from the coefficient for responder status in the Tobit regression. The utility for a non-responder estimated from the Tobit model would be calculated from the reported coefficients as:
Intercept + Baseline EQ-5D + Cirrhosis status (reference is no cirrhosis)

- Thus, for a patient with cirrhosis this equates to [redacted]
- And without cirrhosis it equates to [redacted]
- For the model baseline population, in which 59.78% have cirrhosis, the value would be [redacted]

B31. Priority question. The EAG's clinical experts considered that compensated cirrhosis (CC) is likely to have the same impact on health-related quality of life (HRQoL) as being in METAVIR stages F3 and below. As such, the utility data from MYR 301 seem to produce clinically plausible results to the EAG. Therefore, please:

1. **Include a scenario analysis in the model where the utility values associated with being a complete responder; a partial; and a non-responder (in the F0-F4 states) are estimated with the final Tobit model selected by the company (making sure that all coefficients and respective p-values are reported).**

Company response: A similar scenario to that requested by the EAG is available within the model and was reported as part of the original CS. This scenario applies the baseline EQ-5D extracted directly from the MYR 301 trial (all patients being non-responders at baseline). The scenario can be run by selecting 'MYR 301 trial' in the drop-down selection in cell H10:I10 of sheet 'UTILITY'. The scenario results under our new model base-case are reported below.

Table 28: Cost-effectiveness results for scenario where health-state utility values are informed by MYR 301 EQ-5D analysis

Technologies	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	Base case ICER
BSC	-				
Bulevirtide	[redacted]	4.82	[redacted]	£41,808	£40,562

2. **If pre-treatment with IFN-alfa was found to be a statistically significant predictor of utility in the final Tobit model used by the company, and the utility analysis was performed on the full trial population, please re-run the Tobit model (taking all the necessary steps in the stepwise approach) for the population pre-treated with IFN-alfa and include the resulting utilities as a scenario analysis in the model.**

Company response: As reported in the response to B30, prior treatment with IFN-alfa was not found to be a statistically significant predictor of utility. Furthermore, this is no longer relevant within the context of the overall population, which we consider to be our revised base case in line with our response to A5.

Table 29: Parameter estimates from Tobit model around median, MYR 301 48-week utility analysis

	Estimate	95% CI	p-value
Intercept	[redacted]	[redacted]	[redacted]
Baseline EQ-5D	[redacted]	[redacted]	[redacted]
Liver Cirrhosis	[redacted]	[redacted]	[redacted]
Composite Responder	[redacted]	[redacted]	[redacted]

B32. Priority question. The total QALYs for BSC presented in Table 68 for the QALY shortfall analysis are based on utility values obtained from the meta-analysis of HBV utilities. Please clarify if the utility values and undiscounted life years presented in Table 67 are incorrectly reported (as these are based on the utility data from MYR 301 and the meta-analysis of HCV utilities).

Company response: We would like to thank the ERG for pointing out this error. The utility values reported in Table 67 are incorrect and have been updated in the table below to reflect the HBV utility values.

Table 30: Updated summary of health state benefits and utility values for QALY shortfall analysis (Table 67 from CS)

State	Utility value: mean (standard error)		Undiscounted life years	
	Non-responder	Responder	Non-responder	Responder
F0	0.85	[redacted]	0.00	0.00
F1	0.85	[redacted]	0.00	0.00
F2	0.85	[redacted]	0.93	0.79
F3	0.85	[redacted]	1.92	1.00
Compensated Cirrhosis (F4)	0.76	[redacted]	3.53	1.71
Decompensated cirrhosis	0.46	0.46	1.42	0.01
Hepatocellular carcinoma	0.52	0.52	0.56	0.00
Liver Transplant	0.57	0.57	0.01	0.00
Post-liver transplant	0.67	0.67	0.40	0.00

B33. Priority question. Please clarify why age-related disutility adjustments were not applied in the model. Please run a scenario where age-related utility decrements are applied in the economic model using the published algorithm by Ara and Brazier 2010.

Company response: The option to include age-related utility decrements using the approach requested by the EAG has now been included in the updated model in the SETTINGS sheet cell S23.

Table 31: Cost-effectiveness results for requested scenario B24

Technologies	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	Base case ICER
BSC					
Bulevirtide	[redacted]	4.82	[redacted]	£43,898	£40,562

B34. Priority question. Please provide the meta-analysis report of HBV and HCV utilities. Please note the meta-analysis report sent on the 12 May is for

pharmacological interventions in hepatitis D and not the HBV and HCV utilities.

Company response: A draft report was erroneously provided as part of the original submission, therefore we have provided the final meta-analysis report as part of our clarification question responses.

B35. Please clarify how the sources for the utility decrements associated with AEs were identified and the process for the final selection of values used in the model?

Company response: No appropriate values for utility decrements could be identified from the papers included the HRQoL aspect of the SLR. We therefore looked at previous appraisals in hepatitis B to identify sources that had been previously applied. No utility decrement values could be identified for the adverse events included in the model. We thus identified the utility decrements by searching for the specific utility decrements online, focusing only on papers including UK populations. We would like to draw the EAG's attention to the fact that the model is not sensitive to the AE disutilities, as can be observed when these disutilities are set to 0, that is, removed from the model (Table 32).

Table 32: Cost-effectiveness results for scenario where AE utility decrements are removed

Technologies	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	Base-case ICER
BSC	-				
Bulevirtide	[redacted]	4.82	[redacted]	£40,562	£40,562

Costs

B36. Priority question. The EAG investigated the health state costs from Shephard *et al*. 2006 and these include monitoring resource use as part of the estimates for the CHB health state. As such, the EAG considers the costs of

monitoring may be double counted for both the BSC and bulevirtide arms of the model for the non-cirrhotic (F2 and F3) health states.

a) **Please run a scenario where the health state cost for F3 and below (£886.67) is removed for both the BSC and bulevirtide arms of the model.**

Company response: This scenario has been conducted in the updated model and the results are reported below.

Table 33: Cost-effectiveness results for scenario where health state costs are removed for states F3 and below

Technologies	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	Base-case ICER
BSC	-				
Bulevirtide	[redacted]	4.82	[redacted]	£39,658	£40,562

b) **The EAG could not verify what resources were included to estimate the cost for the F4 health state in Shephard *et al.* 2006. Given the company has estimated specific HDV monitoring costs for patients in the F4 state, this may overlap with the health state cost used in the model. As such, please conduct a scenario where health state costs for health states F4 and below are removed for both the BSC and bulevirtide arms of the model.**

Company response: This scenario has been conducted in the updated model and the results are reported below.

Table 34: Cost-effectiveness results for scenario where health state costs are removed for states F4 and below

Technologies	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	Base-case ICER
BSC	-				
Bulevirtide	[redacted]	4.82	[redacted]	£39,388	£40,562

B37. Priority question. Please clarify why only tenofovir costs were considered for antiviral medication costs.

a) **Please run a scenario analysis where both tenofovir and entecavir are included for antiviral medical costs and justify the proportions used for each drug.**

Company response: It was assumed that all patients would be treated with the same antiviral treatment. Tenofovir costs were selected due to this drug being cheaper than entecavir and it was not expected that this would have a significant impact upon the results. We have tested this assumption by exploring the impact when antiviral costs are removed from the model. As can be seen in Table 35, the ICER under this scenario (£40,450) lies extremely close to the new updated base-case ICER of (£40,562 per QALY). Given that the model is not sensitive to the antiviral costs, we have not provided the requested scenario as we do not have any data to inform the proportions of patients treated with tenofovir and entecavir respectively.

Table 35: Cost-effectiveness results for scenario where antiviral treatment costs are removed

Technologies	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	Base-case ICER
BSC	-				
Bulevirtide	[redacted]	4.82	[redacted]	£40,450	£40,562

B38. Priority question. Please justify why an initial cost to teach patients how to self-administer bulevirtide is not included in the model.

a) **Please run a scenario analysis which includes the cost of teaching a patient how to self-administer bulevirtide.**

Company response: This cost has not been included as this would be borne by the company.

B39. In the NHS reference costs 2019-20, there are three costs for ultrasound elastography using the RD48Z code, which was the code used for both the cost of fibroscan and liver biopsy in the model.

a) **Please clarify why the lowest cost of £43.93 was selected for the cost of fibroscan and liver biopsy in the model.**

Company response: The EAG has correctly pointed out that there are three costs for ultrasound elastography using the RD48Z code in the Diagnostic Imaging sheet within the NHS reference costs. It was assumed that department codes relating to outpatients would be most relevant for costing this resource use item as it falls under routine monitoring for patients eligible for bulevirtide. This therefore ruled out one of the costs for this code (£69.73), which was under the department name 'Imaging: Direct Access'. The 2 remaining costs were both listed under the department name 'Imaging: Outpatient'. Looking at the 'number of examination' column of the reference cost spreadsheet, the number reported under the higher cost was 754 examinations, whilst it was 2807 for the lower cost. Given the significantly larger number of examinations falling under the lower cost category it was thus deemed more representative of the average cost of this procedure. We would like to highlight to the EAG that the model is not very sensitive to these costs, as can be seen when these costs are removed from the model (see Table 36).

Table 36: Cost-effectiveness results for scenario where FibroScan® and liver biopsy unit costs are removed

Technologies	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	Base-case ICER
BSC	-				
Bulevirtide	[redacted]	4.82	[redacted]	£40,482	£40,562

b) **Please clarify why the cost of ultrasound elastography was considered an appropriate proxy for the cost of a liver biopsy, which is an invasive procedure, in the model.**

Company response: We were unable to find an appropriate liver biopsy cost in the NHS reference costs 2019-20, the only liver biopsy cost we could find was 'YG10Z - Percutaneous Transvascular Biopsy of Lesion of Liver'. As this relates to a lesion, we did not think it was appropriate for the cost that would be incurred as part of monitoring. The cost of ultrasound elastography was applied for liver biopsy as this

was the unit cost for fibroscan, which to our understanding is sometimes used interchangeably with liver biopsy – that is, patients will either receive one or the other. We would again like to highlight to the EAG that the model is not very sensitive to these costs, as shown in.

c) **Please clarify why a histopathology cost (DAPS02 - £36.58) was not included for the cost of liver biopsy.**

Company response: This was an error. This cost has been accounted for in the updated model base-case.

d) **Please run a scenario where the higher cost of £129.17 is used for the cost of both fibroscan and liver biopsy and the additional histopathology cost (DAPS02 - £36.58) is included for the cost of liver biopsy.**

Company response: The results for the requested scenario are reported below.

Table 37: Cost-effectiveness results for requested scenario

Technologies	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	Base case ICER
BSC	-				
Bulevirtide	[redacted]	4.82	[redacted]	£40,723	£40,562

e) **Please run a scenario where the higher cost of £129.17 is only used for the cost of liver biopsy and the additional histopathology cost (DAPS02 - £36.58) is also included.**

Company response: The results for the requested scenario are reported below.

Table 38: Cost-effectiveness results for requested scenario

Technologies	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	Base case ICER
BSC	-				
Bulevirtide	[redacted]	4.82	[redacted]	£40,605	£40,562

B40. Please clarify why a haematology cost (DAPS05 - £2.53) was used for the cost of a complete blood count rather than a phlebotomy cost (DAPS08 - £3.67). Please run a scenario using the phlebotomy cost (DAPS08 - £3.67) for the cost of a complete blood count.

Company response: We would like to apologise for this oversight and thank the EAG for highlighting the more appropriate cost. The model base-case has been updated to reflect the phlebetomy cost instead of the original haematology cost.

B41. Tables 60 and 61 in the company submission do not match the data used in the economic model for fibroscan, liver biopsy, alpha-feto protein and hep A IgG. Please confirm which values (model or company submission) are correct and amend as necessary.

Company response: We would like to apologise for this oversight. The values in the company submission are the correct values and the model values have now been updated to the correct values.

Systematic literature review of economic evidence

B42. For the SLR of published cost-effectiveness studies, please provide the references for the two HTA studies that were identified as relevant for inclusion. Additionally, please clarify why these two studies were not included for data extraction in Table 33 of the CS.

Company response: The two HTA studies identified from the SLR have been provided alongside the clarification responses. These studies were not included for data extraction in table 33 of the CS as these studies mainly reported cost data and did not provide all of the information required for table 33. Only studies reporting full economic evaluations were summarised in table 33.

B43. Please clarify if economic evaluation and HRQoL specific search terms were added on top of the clinical SLR search terms outlined in Appendix D of the submission.

Company response: The search strategy was not restricted by study design filters or outcomes. The search strategy included only disease terms and was deliberately

designed to be as broad as possible to cover all relevant studies reporting clinical, economic, quality of life and utility data.

B44. Please clarify why outcomes (such as ICERs, QALYs, etc.) were not included in the economic evaluation and HRQoL PICO eligibility criteria presented in Appendix G and H? Additionally, for the HRQoL search, please clarify if the type of instrument used to estimate utilities was part of the eligibility criteria?

Company response: All relevant economic and HRQoL and utility outcomes were included in the economic and HRQoL and utility SLRs. The search strategy was not restricted by any outcomes. The search strategy included only disease terms and was deliberately designed to be as broad as possible to cover all relevant studies reporting clinical, economic, quality of life and utility outcomes. All studies reporting HRQoL or utility data (irrespective of the instrument or method) for the population of interest were included in the review. However, we have updated Table 86 and Table 87 from the original company submission to reflect the relevant outcomes.

Table 39: Update of table 86 from CS, PICO eligibility criteria for cost-effectiveness studies

PICO	Inclusion Criteria
Population	• Adults with CHD who have compensated liver disease
Interventions	• Only pharmacological interventions
Comparators	• No restriction
Study Design	Economic evaluations • Cost-effectiveness analysis (CEA) • Cost-utility analysis (CUA) • Cost-minimisation analysis (CMA) • Cost-consequence analysis (CCA) • Cost-benefit analysis (CBA) • Cost-offset analysis (COA) • Budget impact analysis (BIA) Cost/resource use • Studies reporting cost and/or resource use data
Outcomes	Economic evaluations • Costs • Costs per outcome • Quality adjusted life years (QALYs) • Life years gained (LYG)

	• Incremental cost effectiveness ratios (ICERs) Cost/resource use • Measures of costs • Measures of resource use
Language	• Studies published in English language or having English abstract or summary
Publication timeframe	• Original SLR: Database inception to October 2020 • *Update 1: For the April 2021 update, articles were required to have been published in or after 2020* • Update 2: *For the December 2021 update, articles were required to have been published in 2021 (For the sufficient overlap with last update)*

Table 40: Update of table 87, PICO eligibility criteria for HRQoL SLR

PICOS	**Inclusion Criteria**
Participants	• Adults with chronic hepatitis D who have compensated liver disease
Interventions	• Only pharmacological interventions
Comparators	• No restriction
Study Design	• Cohort studies including historical and nested case-control • Retrospective and prospective observational studies • Cross-sectional studies • Registry/database-based studies • Controlled clinical trials • Single-arm studies
Outcomes	• Any HRQoL outcomes • Utilities/disutilities/QALYs for health states or adverse events • Mapping algorithms
Language	• Studies published in English language or having English abstract or summary
Publication timeframe	• Database inception to October 2020 • Update 1: For the March 2021 update, articles were required to have been published in or after 2020 • Update 2: For the December 2021 update, articles were required to have been published in 2021 (For the sufficient overlap with last update)

Section C: Textual clarification and additional points

C1. Please clarify how the user defined cells can be activated in the economic model.

Company response: The economic model has undergone significant adaptation since it was originally built. As such, the user defined cells that appear on the inputs worksheets such as ‘COSTS’, ‘NAT_HIS’ are not linked directly to the parameters (‘INPUTS’) sheet. To activate user defined values, the parameter values in the ‘user defined value’ column (column I) will need to be changed directly in the ‘INPUTS’ sheet *or* the cells in column I need to reference the user-defined cell (from the individual sheets e.g. ‘COSTS’) for the respective parameter. This will then update the live value in column J of the ‘INPUTS’ sheet.

References

1. Jacobson IM, Washington MK, Buti M, Thompson A, Afdhal N, Flisiak R, et al. Factors Associated With Persistent Increase in Level of Alanine Aminotransferase in Patients With Chronic Hepatitis B Receiving Oral Antiviral Therapy. Clin Gastroenterol Hepatol [Internet]. 2017 Jul 1 [cited 2022 Feb 10];15(7):1087-1094.e2. Available from: https://pubmed.ncbi.nlm.nih.gov/28215615/
2. Enomoto H, Aizawa N, Nishikawa H, Ikeda N, Sakai Y, Takata R, et al. Relationship Between Hepatic Steatosis and the Elevation of Aminotransferases in HBV-Infected Patients With HBe-Antigen Negativity and a Low Viral Load. Medicine (Baltimore) [Internet]. 2016 Apr 1 [cited 2022 Feb 10];95(17). Available from: https://pubmed.ncbi.nlm.nih.gov/27124068/
3. Ghany MG, Feld JJ, Chang KM, Chan HLY, Lok ASF, Visvanathan K, et al. Serum Alanine Aminotransferase Flares In Chronic Hepatitis B: The Good and The Bad. lancet Gastroenterol Hepatol [Internet]. 2020 Apr 1 [cited 2022 Jun 9];5(4):406. Available from: /pmc/articles/PMC7158588/
4. Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology [Internet]. 2018 Apr 1 [cited 2021 Oct 26];67(4):1560–99. Available from: https://pubmed.ncbi.nlm.nih.gov/29405329/
5. Lampertico P, Agarwal K, Berg T, Buti M, Janssen HLA, Papatheodoridis G, et al. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol [Internet]. 2017 Aug 1 [cited 2021 Oct 26];67(2):370–98. Available from: https://pubmed.ncbi.nlm.nih.gov/28427875/
6. Jacobson IM, Washington MK, Buti M, Thompson A, Afdhal N, Flisiak R, et al. Factors Associated With Persistent Increase in Level of Alanine Aminotransferase in Patients With Chronic Hepatitis B Receiving Oral Antiviral Therapy. Clin Gastroenterol Hepatol [Internet]. 2017 Jul 1 [cited 2022 Jun 8];15(7):1087-1094.e2. Available from: https://pubmed.ncbi.nlm.nih.gov/28215615/
7. GSI - Data on file. ALT Visualisation Graphs Week 48. 2022.
8. GSI - Data on file. MYR 301 Clinical Study Report. 2022;
9. Farci P, Niro GA. Current and future management of chronic hepatitis D. Gastroenterol Hepatol [Internet]. 2018 Jun 1 [cited 2021 Oct 26];14(6):342–51. Available from: /pmc/articles/PMC6111511/
10. GSI - Data on file. MYR 202 Clinical Study Report. 2019;
11. European Medicines Agency. Hepcludex [Internet]. 2021 [cited 2021 Oct 26]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/hepcludex
12. ClinicalTrials.gov. Myrcludex B in Combination With Peginterferon Alfa-2a Versus Peginterferon Alfa-2a Alone in Patients With Chronic Viral Hepatitis B With Delta-agent [Internet]. [cited 2022 Feb 25]. Available from: https://clinicaltrials.gov/ct2/show/NCT02888106
13. Medicines and Healthcare Products Regulatory Agency (MHRA). Hepcludex - Summary of Product Characteristics (SmPC) [Internet]. 2021 [cited 2022 Mar 25]. Available from: https://mhraproducts4853.blob.core.windows.net/docs/ccbbd004d098f9661d5ba8c7bb961d80545bec1e

14. Dienstag JL, Ghany MG, Morgan TR, Di Bisceglie AM, Bonkovsky HL, Kim HY, et al. A prospective study of the rate of progression in compensated, histologically advanced chronic hepatitis C. Hepatology. 2011;54(2):396–405.
15. 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 [Internet]. 2020 Sep 1 [cited 2021 Oct 26];73(3):533–9. Available from: https://pubmed.ncbi.nlm.nih.gov/32151618/
16. Bermingham SL, Hughes R, Fenu E, Sawyer LM, Boxall E, T.Kennedy P, et al. Cost-Effectiveness Analysis of Alternative Antiviral Strategies for the Treatment of HBeAg-Positive and HBeAg-Negative Chronic Hepatitis B in the United Kingdom. Value Heal [Internet]. 2015;18(6):800–9. Available from: http://dx.doi.org/10.1016/j.jval.2015.05.007
17. Fattovich G. Natural history and prognosis of hepatitis B [Internet]. Vol. 23, Seminars in Liver Disease. Copyright © 2002 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA. Tel.: +1(212) 584-4662; 2003 [cited 2021 Oct 26]. p. 47–58. Available from: http://www.thieme-connect.com/products/ejournals/html/10.1055/s-2003-37590
18. Dakin H, Fidler C, Harper C. Mixed treatment comparison meta-analysis evaluating the relative efficacy of nucleos(t)ides for treatment of nucleos(t)ide-naive patients with chronic hepatitis B. Value Heal [Internet]. 2010;13(8):934–45. Available from: http://dx.doi.org/10.1111/j.1524-4733.2010.00777.x
19. Wong WWL, Woo G, Jenny Heathcote E, Krahn M. Cost effectiveness of screening immigrants for hepatitis B. Liver Int Off J Int Assoc Study Liver. 2011 Sep;31(8):1179–90.
20. Liaw Y -F, Lin D -Y, Chen T -J, Chu C -M. Natural course after the development of cirrhosis in patients with chronic type B hepatitis: a prospective study. Liver. 1989;9(4):235–41.
21. Veenstra DL, Sullivan SD, Dusheiko GM, Jacobs M, Aledort JE, Lewis G, et al. Cost-effectiveness of peginterferon α-2a compared with lamivudine treatment in patients with HBe-antigen-positive chronic hepatitis B in the United Kingdom. Eur J Gastroenterol Hepatol. 2007;19(8):631–8.
22. Da BL, Heller T, Koh C. Hepatitis D infection: From initial discovery to current investigational therapies. Gastroenterol Rep. 2019;7(4):231–45.
23. Bermingham SL, Hughes R, Fenu E, Sawyer LM, Boxall E, T.Kennedy P, et al. Cost-Effectiveness Analysis of Alternative Antiviral Strategies for the Treatment of HBeAg-Positive and HBeAg-Negative Chronic Hepatitis B in the United Kingdom. Value Heal. 2015;18(6):800–9.
24. Fattovich G, Giustina G, Schalm SW, Hadziyannis S, Sanchez-Tapias J, Almasio P, et al. Occurrence of hepatocellular carcinoma and decompensation in Western European patients with cirrhosis type B. Hepatology. 1995;21(1):77–82.
25. Fattovich G, Giustina G, Christensen E, Pantalena M, Zagni I, Realdi G, et al. Influence of hepatitis delta virus infection on morbidity and mortality in compensated cirrhosis type B. Gut [Internet]. 2000 [cited 2021 Oct 26];46(3):420–6. Available from: /pmc/articles/PMC1727859/
26. Iloeje UH, Yang HI, Jen CL, Su J, Wang LY, You SL, et al. Risk and Predictors of Mortality Associated With Chronic Hepatitis B Infection. Clin Gastroenterol Hepatol. 2007;5(8):921–31.
27. NHS Blood & Transplant. Organ and Tissue Donation and Transplantation in the UK 2020-2021. 2021; Available from:

https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/24053/activity-report-2020-2021.pdf
28. NHS Blood & Transplant. Organ and Tissue Donation and Transplantation in the UK 2020-2021. 2021;
29. Gheorghe L, Iacob S, Simionov I, Vădan R, Gheorghe C, Iacob R, et al. Natural history of compensated viral B and D cirrhosis. Rom J Gastroenterol. 2005;14(4):329–35.

Summary of changes to model base-case

Model change	Cell location
Change of model population from the PEG-experienced sub-group from MYR 301 to the whole trial population	Drop-down in cells F8:G8 in sheet 'CLINICAL'
Change of hazard ratios (HRs) for disease progression in complete responders from 0.001 to 0	Cells F58:F62 in sheet 'DROPDOWNS'
Change of complete responder HR from F4 to liver-related death to be equal to the HR for partial responders (0.22).	Cell F63 in sheet 'DROPDOWNS'
Inclusion of histopathology cost as part of the unit cost for livery biopsy	Cell I87 in sheet 'COSTS'
Unit cost of complete blood count has been updated to a phlebotomy cost	Cell I91 in sheet 'COSTS'

B.3.10 Base-case results

Base-case incremental cost-effectiveness analysis results

Table 1: Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
BSC	[redacted]	8.14	[redacted]	-				
Bulevirtide	[redacted]	12.96	[redacted]	[redacted]	4.82	[redacted]	£40,562	£40,562

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 2: Net health benefit

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £24,000	NHB at £36,000
BSC	[redacted]	[redacted]	-			
Bulevirtide	[redacted]	[redacted]	[redacted]	[redacted]	-3.20	-0.59

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; NHB, net health benefit

B.3.11 Exploring uncertainty

Probabilistic sensitivity analysis

Table 3: Probabilistic cost-effectiveness results

Technologies	Total costs (£)	Total QALYs	Incremental. costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
BSC	[redacted]	[redacted]				
Bulevirtide	[redacted]	[redacted]	[redacted]	[redacted]	£42,239	£42,239

Figure 1: PSA scatterplot

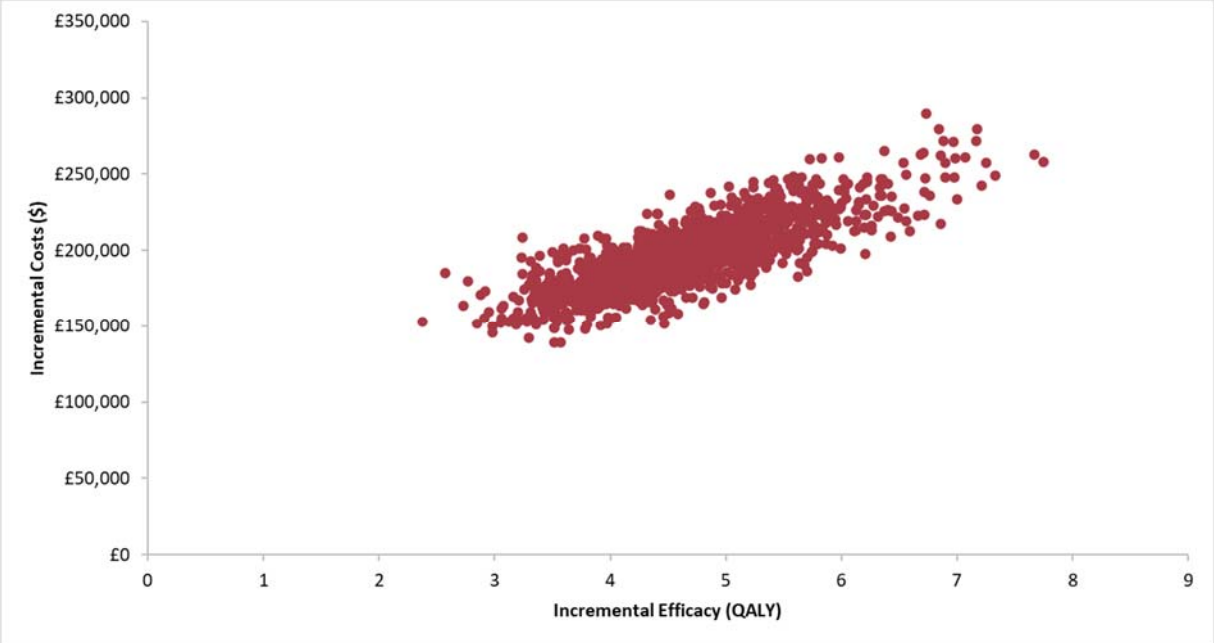
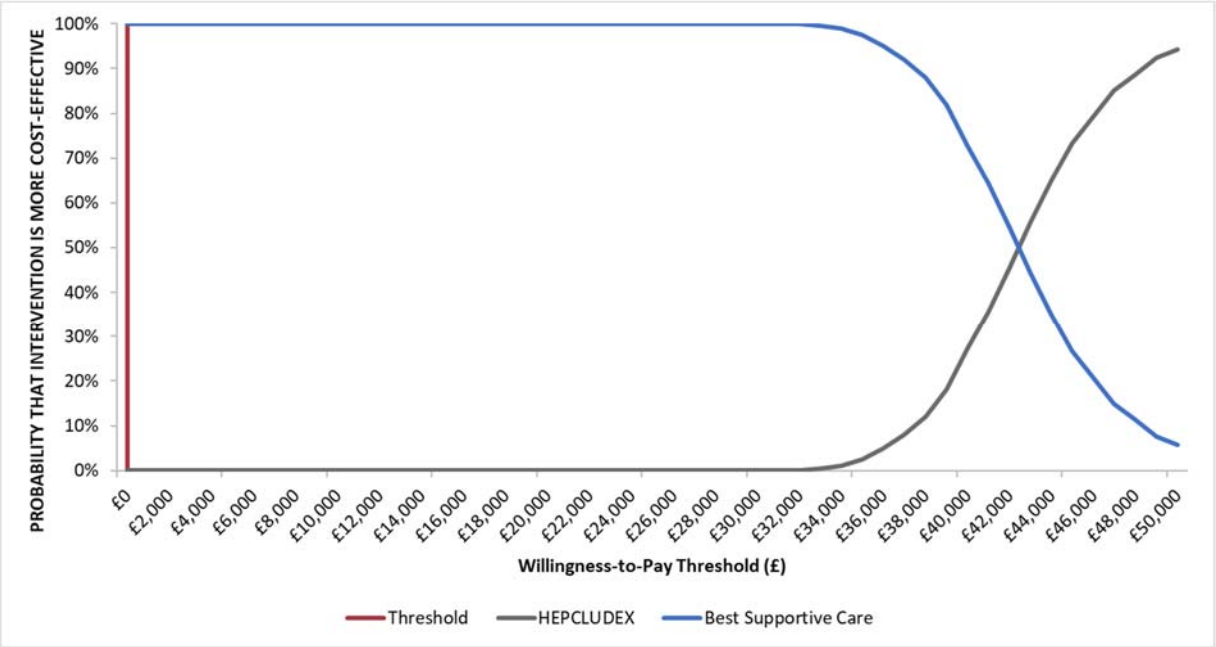


Figure 2: Cost-effectiveness acceptability curve, bulevirtide vs BSC



Deterministic sensitivity analysis

Figure 3: OWSA results, bulevirtide vs BSC

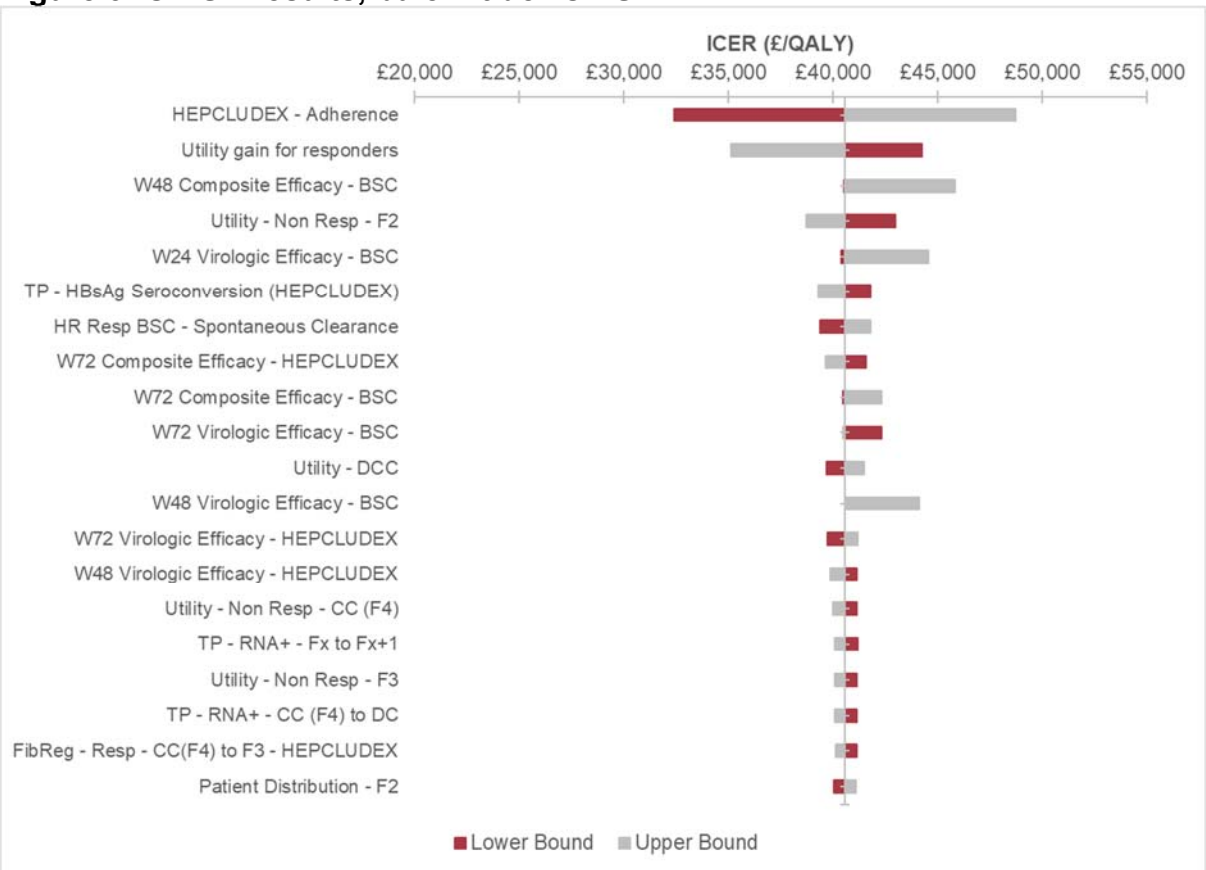


Table 4: OWSA results, bulevirtide vs BSC

Parameter	Lower bound ICER	Upper bound ICER	Difference
HEPCLUDEX - Adherence	£32,417	£48,707	£16,290
Utility gain for responders	£44,259	£35,117	£9,142
W48 Composite Efficacy - BSC	£40,508	£45,841	£5,333
Utility - Non Resp - F2	£42,955	£38,713	£4,242
W24 Virologic Efficacy - BSC	£40,407	£44,572	£4,165
TP - HBsAg Seroconversion (HEPCLUDEX)	£41,789	£39,291	£2,499
HR Resp BSC - Spontaneous Clearance	£39,380	£41,788	£2,408
W72 Composite Efficacy - HEPCLUDEX	£41,582	£39,642	£1,940
W72 Composite Efficacy - BSC	£40,467	£42,325	£1,858
W72 Virologic Efficacy - BSC	£42,325	£40,470	£1,856
Utility - DCC	£39,701	£41,496	£1,795
W48 Virologic Efficacy - BSC	£42,385	£44,099	£1,714
W72 Virologic Efficacy - HEPCLUDEX	£39,746	£41,159	£1,414
W48 Virologic Efficacy - HEPCLUDEX	£41,153	£39,869	£1,284
Utility - Non Resp - CC (F4)	£41,129	£40,010	£1,118
TP - RNA+ - Fx to Fx+1	£41,198	£40,093	£1,105
Utility - Non Resp - F3	£41,151	£40,070	£1,080
TP - RNA+ - CC (F4) to DC	£41,145	£40,074	£1,071
FibReg - Resp - CC(F4) to F3 - HEPCLUDEX	£41,130	£40,105	£1,025
Patient Distribution - F2	£40,059	£41,070	£1,011

Scenario analysis

Table 5: Scenario analyses results

Structural assumption	Base-case scenario	Other scenarios considered	Incremental costs	Incremental QALYs	ICER vs. BSC
Base-case			[redacted]	[redacted]	**£40,562**
Patients' baseline fibrosis status	F2-F4	F3-F4	[redacted]	[redacted]	£38,317
Inclusion of utility gain for responders	Included	Excluded	[redacted]	[redacted]	£44,259
Fibrosis regression	Included	Excluded	[redacted]	[redacted]	£46,253
Hazard ratios for progression in complete responders	Value of 0	Hazard ratios are half of that of the partial responders	[redacted]	[redacted]	£43,446
Definition of responder	Composite	Virologic	[redacted]	[redacted]	£48,270
Extrapolation of 48-week MYR 301 response data	Yes	No	[redacted]	[redacted]	£41,468
Source of non-responder health state utility values for mild-moderate health states	CHB meta-analysis for F0-F4	MYR 301 for F0-F4	[redacted]	[redacted]	£41,808
Source of health state utility values for all non-responder health states	CHB meta-analysis	Chronic HCV meta-analysis	[redacted]	[redacted]	£41,970

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Bulevirtide for treating chronic hepatitis D [ID3732]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**British Association for Sexual Health and HIV**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	1. BASHH represents healthcare workers and scientists in the field of Sexual health and HIV-BBV medicine The aims of BASHH are • To promote, encourage and improve the study and practice of diagnosing, treating and managing sexually transmitted infections, HIV and other sexual health problems • To innovate and deliver excellent tailored education and training to health care professionals, trainers and trainees in the UK • To determine, monitor and maintain standards of governance in the provision of sexual health and HIV care • To advance public health in relation to sexually transmitted infections, HIV and other sexual health problems • To champion and promote good sexual health and provide education to the public BASHH incomes comes from investments, membership subscriptions, and educational events.
4b. Has the organisation received any funding from the manufacturer(s) of the	**NO**

technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**NO**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To achieve suppressed virological response (SVR) of Hepatitis D Virus (HDV), which will reduce progression of liver fibrosis and reduce the risks of hepatocellular carcinoma and liver-related morbidity and mortality in people living with Hepatitis B Virus (HBV) and HDV co-infection.

7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Achievement of SVR and reduced viral load.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, people living with HBV-HDV do not currently have access to efficacious and tolerable medication for HDV suppression.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	As per NICE Guidelines for HBV Antiviral treatment sections 1.5.45 - 1.5.47, with pegylated interferon.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	As per NICE Guidelines for HBV Antiviral treatment sections 1.5.45 - 1.5.47, with pegylated interferon.
• Is the pathway of care well defined? Does it	Pathway to treatment is defined by NICE guidelines

vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	The technology would increase access to treatment for people living with HBV-HDV.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The technology will be used in a similar way to current therapy.
• How does healthcare resource use differ between the technology and current care?	The technology will be used in a similar way to current therapy.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The technology should be used in Specialist Hepatitis clinics.

• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Investment is needed in training staff, providing patient information leaflets and peer support.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, the technology will provide clinically meaningful benefits.
• Do you expect the technology to increase length of life more than current care?	Yes
• Do you expect the technology to increase health-related quality of life more than current care?	Yes
12. Are there any groups of people for whom the technology would be more or	People living with HBV-HDV, especially Black African people who are disproportionality affected by these viruses.

less effective (or appropriate) than the general population?	
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Technology will be similar to use as current therapies
14. Will any rules (informal or formal) be used to start or stop treatment with the technology?	No additional testing required.

Do these include any additional testing?	
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	I expect the technology to make a significant improvement in efficacy in achieving HDV SVr and reducing liver-related health problems.
• Is the technology a 'step-change' in the	Yes

management of the condition?	
• Does the use of the technology address any particular unmet need of the patient population?	Yes there is an unmet need in achieving HDV SVR
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Side effects are expected to be minimal and not have adverse outcomes.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Clinical trials reflect current UK practice.
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important	Most important outcomes were achievement of HDV SVR with this treatment

outcomes, and were they measured in the trials?	
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Yes SVR is a good surrogate measure for liver-related health outcomes
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No additional adverse events
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of any previous	No

NICE technology appraisal guidance in this area?	
21. How do data on real-world experience compare with the trial data?	N/A
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	We need to ensure people without English as a first language have equitable access – this means using interpreters, peer support, patient information leaflets and posters in their languages.
22b. Consider whether these issues are different from issues with current care and why.	This will require a scaling up of current services to ensure we offer treatment to all those who need it and we are testing those at risk
Key messages	

23. In up to 5 bullet points, please summarise the key messages of your submission.

- New efficacious treatment, which helps achieve HDV SVR
- Treatment has very good and well tolerated profile
- SVR is a good surrogate marker for improving liver-related health outcomes
- Equitable access is needed for all people living with HBV-HDV
- Additional resources will include peer support, patient information leaflets and posters

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Bulevirtide for treating chronic hepatitis D [ID3732]

Professional organisation submission

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**Royal College of Pathologists**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The Royal College of Pathologists is a professional membership organisation with charitable status, concerned with all matters relating to the science and practice of pathology. It is a body of its Fellows, Affiliates and trainees, supported by the staff who are based at the College's London offices. The College is a charity with over 11,000 members worldwide. The majority of members are doctors and scientists working in hospitals and universities in the UK. The College oversees the training of pathologists and scientists working in 17 different specialties, which include cellular pathology, haematology, clinical biochemistry and medical microbiology. Although some pathologists work in laboratories, many work directly with patients in hospitals and the community. Together they are involved in the majority of all diagnoses, as well as playing an important role in disease prevention, treatment and monitoring. If you have ever had a blood test, cervical smear or tissue biopsy, a pathologist will have been involved in your care. The College is funded from subscriptions, examinations and related fees, investment income, grants from outside bodies and charitable donations and legacies.

4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	**No**
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve	To stop progression, liver fibrosis, cirrhosis, liver cancer and death.

mobility, to cure the condition, or prevent progression or disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	normalisation of liver function tests, clearance of HDV viral load in blood
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	By specialists, using PEG IFN. Or not treated.
• Are any clinical guidelines used in the	EASL 2017 guideline for treatment of chronic hepatitis D.

treatment of the condition, and if so, which?	
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There is variation between professionals in Wales in testing for the condition in the first place so there may be undetected cases. The EASL guidance is not well defined for Hepatitis B – D coinfection and therefore may lead to variation in practice. There may be uncertainty about using NA and PEG IFN together. The Pegasys (PEG IFN) product sheet does not include hepatitis D treatment information. Clinicians may not want to use current treatment PEG IFN due to side effects.
• What impact would the technology have on the current pathway of care?	The drug would be a specific antiviral against Hepatitis D and provide another treatment option to PEG IFN.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The technology is not currently used in Wales, or in the UK.
• How does healthcare resource use differ between the technology and current care?	Proposed less healthcare resource with fewer patient clinic visits due to fewer side effects, and disease progression from the technology vs current care. There may be more healthcare resource needed for cost of the technology as clinicians test for the condition more as awareness increases and availability of a specific antiviral.

• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care and specialist hepatitis clinics
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Investment in guidelines and training. Investment in mapping the prevalence of Hepatitis D in the UK.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
• Do you expect the technology to increase length of life more than current care?	Yes
• Do you expect the technology to increase health-related quality of life more than current care?	Yes

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The technology would be more appropriate in hepatitis B and D coinfected patients
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	The technology should be easier as it is administered over 6 months rather than current treatment which is 48 weeks.

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Hepatitis D and Hepatitis B testing will be required, and liver function test monitoring. Hepatitis D viral load monitoring may be required as other additional testing
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	The technology may result in patients suffering fewer side effects than PEG IFN
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	The technology has the potential to minimise side effects of hepatitis D treatment. Currently patients would not be treated who suffer side-effects on current treatment.

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	The technology is a step change
• Does the use of the technology address any particular unmet need of the patient population?	The technology may encourage clinicians to diagnose the condition
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Fewer side effects anticipated with the new technology
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes

• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Few sides effects. Similar relapse rate as with current treatment Pegylated IFN
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
20. Are you aware of any new evidence for the comparator	

treatment(s) since the publication of any previous NICE technology appraisal guidance in this area?	
21. How do data on real-world experience compare with the trial data?	
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Availability of testing for affected patients. Availability of the treatment. Patients' ability to administer the drug
22b. Consider whether these issues are different from issues with current care and why.	New technology requires daily administration which may have resource implications if they patient is unable to self-administer. Current treatment with PEG IFN is once weekly administration.
Key messages	

23. In up to 5 bullet points, please summarise the key messages of your submission.

- Fewer side effect profile
- Novel antiviral targeted at the virus,
- Increased awareness and testing for hepatitis D
- New treatment option

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Bulevirtide for treating chronic hepatitis D [ID3732]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**UK Clinical Pharmacy Association**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	UKCPA provides practitioner-led education and training for the pharmacy workforce
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	**No**

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	- Cure of hepatitis D –sustained virological response with undetectable HDV RNA and surface Ag loss - Biochemical response with normalisation of ALT - Prevent progression of liver disease and prevention of development of Hepatocellular carcinoma
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	Sustained virological response 24 weeks after the treatment stops and surface antigen loss OR a 2 log10 reduction in HDV RNA.

x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. There are currently no licensed treatment options for hepatitis D. Hepatitis D ca lead to rapid progression to cirrhosis, hepatic decompensation and liver cancer when left untreated.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Using peginterferon alfa-2a which is unlicensed. The recommended course of treatment is 48 weeks.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	- Hepatitis B (chronic): diagnosis and management Clinical guideline [CG165]Published: 26 June 2013 Last updated: 20 October 2017 - Sarin SK, et al. Hepatol Int 2016;10:1-98; - EASL. Clinical Practice Guidelines on the managementvof hepatitis B virus infection J Hepatol 2017;67:370–98; - AASLD 2018 Hepatitis B Guidance, Hepatology 2018;67:1560–99; - EACS Guidelines 2021 v11.0.vvAvailable at: https://www.eacsociety.org/guidelines/eacs-guidelines/ (all accessed January 2022).
• Is the pathway of care well defined? Does it vary or are there	There is some variation in screening for HDV.

differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	It would improve treatment pathways and referral into tertiary centres who are best placed to treat this rare but significant infection.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes
• How does healthcare resource use differ between the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist clinics who can undertake appropriate monitoring
• What investment is needed to introduce the	

technology? (For example, for facilities, equipment, or training.)	
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
• Do you expect the technology to increase length of life more than current care?	Yes
• Do you expect the technology to increase health-related quality of life more than current care?	Yes
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	N/A

The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	No. It remains as a subcutaneous injection which is the same as current care with pegylated interferon.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Not different to current standard of care. HDV serology will need to be closely monitored as will liver function tests including bilirubin.

15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	N/A
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes
• Is the technology a 'step-change' in the management of the condition?	Yes as it is the first in class and only licensed treatment for HDV
• Does the use of the technology address any	Yes

particular unmet need of the patient population?	
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Most common side effect reported is elevation in total bile salts. This was not reported to have a significant impact on patient QOL.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	HDV RNA reduction and Sag seroconversion and normalisation of ALT which were reported in the trials.
• If surrogate outcome measures were used, do they adequately predict	N/A

long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	N/A
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of any previous NICE technology appraisal guidance in this area?	N/A
21. How do data on real-world experience compare with the trial data?	N/A

Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	N/A
Key messages	
23. In up to 5 bullet points, please summarise the key messages of your submission. • First in class and effective treatment option for an orphan disease with limited treatment options currently available • Meets unmet need • Should be prescribed by specialist centres experienced in managing patients with HDV with access to diagnostics. • Limited side effect profile • Will fit into current treatment pathway and standard of care pathways	

Thank you for your time.

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Bulevirtide for treating chronic hepatitis D

STA Report

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 13/37/00.

Title:	Bulevirtide for treating chronic hepatitis D
Produced by:	BMJ Technology Assessment Group (BMJ TAG)
Authors:	Steve Edwards, Director of Health Technology Assessment, BMJ-TAG, London Charlotta Karner, Clinical Evidence Manager, BMJ-TAG, London Mariana Bacelar, Principal Health Economist, BMJ-TAG, London Nicole Downes, Senior Clinical Evidence Analyst, BMJ-TAG, London Ben Farrar, Senior Clinical Evidence Analyst, BMJ-TAG, London Tracey Jhita, Health Economics Manager, BMJ-TAG, London
Correspondence to:	Steve Edwards, BMJ-TAG, BMJ, BMA House, Tavistock Square, London, WC1H 9JR.
Date completed:	07/07/2022
Source of funding:	This report was commissioned by the NIHR Evidence Synthesis Programme as project number 13/37/00.
Declared competing interests of the authors	No competing interests were declared which affect the impartiality of this report. BMJ Technology Assessment Group (BMJ-TAG) and the editorial team of The BMJ work independently to one another. The views and opinions expressed in this report are those of the BMJ-TAG.
Acknowledgments:	The EAG would like to thank Prof William Rosenberg, Professor of Liver Diseases at University College London, and Prof Matthew Cramp, Professor of Hepatology at the South West Liver Unit, Derriford Hospital, for providing clinical advice throughout the project, and for providing feedback on the clinical sections of the report. The EAG would also like to thank Dr Kosh Agarwal, Consultant Hepatologist and Transplant Physician at Institute of Liver Studies, Kings College Hospital for providing feedback on the clinical sections of the report.
Rider on responsibility for report:	The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.
Report reference:	Order of authors [Team lead, clinical lead, health economic lead, clinical support, health economic support]. [Title of NICE final scope]: A Single Technology Appraisal. BMJ Technology Assessment Group, [year].

Contribution of authors:

Steve Edwards	Critical appraisal of the company's submission; validated the statistical analyses; provided feedback on all versions of the report. Guarantor of the report
Charlotta Karner	Critical appraisal of the company's submission and the clinical evidence; drafted and reviewed the clinical sections of the report
Nicole Downes	Critical appraisal of the company's submission and the clinical evidence; drafted the background section and critiqued the decision problem
Ben Farrar	Critical appraisal of the company's submission and the clinical evidence; cross checking and critiqued the company's literature review and drafted the clinical results section
Mariana Bacelar	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections
Tracey Jhita	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and assisted with drafting the economic sections

All authors read and commented on draft versions of the EAG report.

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List of Abbreviations

µg	Microgram
AASLD	American Association for the Study of Liver Diseases
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BLV	Bulevirtide
BMI	Body mass index
BSC	Best supportive care
CC	Compensated cirrhosis
CEAC	Cost-effectiveness acceptability curve
CfB	Change from baseline
CG	Clinical guidelines
CHB	Chronic hepatitis B
CHD	Chronic hepatitis delta
CI	Confidence interval
CRD	Centre for Reviews and Dissemination
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events
d	Day
DCC	Decompensated cirrhosis
DMA	Direct meta-analysis
DT	Delayed treatment
EAG	Evidence assessment group
EASL	European Association for the Study of the Liver
EC	European Commission
ECG	Electrocardiogram
EMA	European Medicines Agency
EOS	End of study
EPAR	European public assessment report
EQ-5D	EuroQoL-5 Dimension
EQ-5D-3L	EuroQoL-5 Dimension 3 Levels
FACIT-F	Functional assessment of chronic illness therapy-fatigue
FAS	Full analysis set
FDA	Food and Drug Administration
GGT	Gamma-glutamyl transferase
GSI	Gilead Sciences, Inc.
HBeAg	Hepatitis B e-antigen
HBsAg	Hepatitis B surface antigen

HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCRU	Healthcare resource utilisation
HCV	Hepatitis C virus
HDAg	Hepatitis delta antigen
HDV	Hepatitis delta virus
HIV	Human immunodeficiency virus
HQLQ	Hepatitis Quality of Life Questionnaire™
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
ICF	Informed consent form
IFN	Interferon
IPD	Individual patient data
IQR	Interquartile range
kPa	Kilopascal
LOCF	Last observation carried forward
LOD	Limit of detection
LT	Liver transplantion
LYG	Life years gained
MedDRA	Medical Dictionary for Regulatory Activities
MEF	Missing equals failure
mg	Milligram
MHRA	Medicines and Healthcare products Regulatory Agency
mITT	Modified intention-to-treat
n/miss	Number of patients with evaluable/missing data
NA	Nucelos(t)ide analogue
NC	Non-cirrhotic
NHB	Net health benefit
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NTCP	Sodium taurocholate co-transporting polypeptide
OLS	Ordinary least squares
ONS	Office for National Statistics
OR	Odds ratio
OWSA	One-way deterministic sensitivity analysis
PAS	Patient access scheme
PCR	Polymerase chain reaction
PEG-IFN	Peginterferon alfa-2a
PIM	Promising innovative medicine
PLT	Post-liver transplant

PO	Per oral
PP	Per protocol
PPAS	Per protocol analysis set
PRO	Patient reported outcome
PSA	Probabilistic sensitivity analysis
Q1	First quartile
Q3	Third quartile
QALY	Quality-adjusted life year
QoL	Quality of life
RNA	Ribonucleic acid
SAE	Serious adverse event
SAS	Safety analysis set
SC	Subcutaneous
SD	Standard deviation
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
TDF	Tenofovir
TEAE	Treatment-emergent adverse event
UK	United Kingdom
ULN	Upper limit of normal
VAS	Visual Analogue Scale
VR	Virologic resistance
WK	Weekly
WPAI	Work productivity and activity impairment
WTP	Willingness-to-pay

1 Executive summary

This summary provides a brief overview of the key issues identified by the evidence review group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Section 1.3 explains the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table 1. Summary of key issues

Issue	Summary of issue	Report sections
1	Generalisability of trial population to the narrower population focused on by the company	2.3.1, 3.2.2, 3.3.2, 3.4, 4.2.2
2	Generalisability of trial population to UK patients	2.3.1, 3.2.2, 4.2.2
3	Uncertainty in the extrapolations beyond the observed trial data	2.3.2, 3.4, 4.2.4, 4.2.10
4	Modelling of HCC	4.2.4
Abbreviations:		

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increasing the probability of response (complete and partial) up to week 72 in the model, which in turn leads to a lower probability of cirrhotic decompensation and hepatocellular carcinoma and better overall survival.
- Halting the probability of fibrosis progression (and increasing the probability of fibrosis regression), which in turn leads to a lower probability of cirrhotic decompensation and hepatocellular carcinoma and better overall survival.

Overall, the technology is modelled to affect costs by:

- Its higher unit cost compared to best supportive care.
- Decreasing the probability of compensated cirrhosis; cirrhotic decompensation; and hepatocellular carcinoma and the higher costs of treatment and disease management associated with these states.

The modelling assumptions that have the greatest effect on the ICER are:

- The source used to reflect age and cirrhosis distribution at baseline in the model (i.e., external literature or the MYR 301 population).
- The assumption that complete responders have a utility gain (in all F-states) compared to partial responders and non-responders.
- Adjusting the utilities for patients' age as per Ara and Brazier.[1]

1.3 Summary of the EAG's key issues

Table 2. Issue 1 Generalisability of trial population to the narrower population focused on by the company

Report section	2.3.1, 3.2.2, 3.3.2, 3.4, 4.2.2
Description of issue and why the EAG has identified it as important	The company has focused their submission on a subpopulation of the key trial (MYR 301); patients with CHD who have compensated liver disease and evidence of significant fibrosis (METAVIR stage greater than or equal to F2), whose disease has responded inadequately to IFN-based therapy, or who are ineligible to receive IFN-based therapy due to intolerance or contraindication. Overall, the EAG considers this population to be reasonable given this represents a subset of patients covered in the conditional marketing authorisation with a particularly high unmet need in terms of treatment options. However, it is unclear to what extent the effectiveness of bulevirtide differs between the full trial population and the narrower population the company is focusing on as data limited to the narrower population are not available from the trial; data on METAVIR fibrosis stage was only available for [redacted] of participants and although subgroup data are available for participants previously treated with IFN therapy, this did not capture participants who were intolerant or for whom IFN therapy was contraindicated. It may be easier for patients with lower METAVIR fibrosis stage (F0 or F1) to achieve biochemical response as they are likely to be closer to the ALT normalisation threshold. This would cause a potential overestimate of the efficacy of bulevirtide 2 mg compared with BSC in the full trial population compared with patients with METAVIR fibrosis stage of F2 or above, i.e., the population the company is focusing on. In addition, for participants with METAVIR fibrosis staging data available at baseline there was a relatively large imbalance between the treatment arms in the number of patients with the lower stages of fibrosis (F0 and F1), which may exacerbate the potential overestimate of the bulevirtide effectiveness in the full trial population. However, the pre-specified and stratified cirrhotic subgroup, defined as METAVIR fibrosis stage F4, should be unaffected by this imbalance. The subgroup analyses of cirrhotic and non-cirrhotic patients show a numerical difference with a larger proportion of patients achieving a combined

	response with bulevirtide treatment among those without cirrhosis compared to those with cirrhosis at baseline.
What alternative approach has the EAG suggested?	The EAG recommends that the company includes a scenario analysis in the model focused on the cirrhotic subgroup at Technical Engagement.
What is the expected effect on the cost-effectiveness estimates?	Given that the treatment effect with bulevirtide is lower in the cirrhotic subgroup, restricting the model population to the latter will increase the ICER.
What additional evidence or analyses might help to resolve this key issue?	As above.

Abbreviations: ALT, alanine aminotransferase; CHD, chronic hepatitis D; EAG, evidence review group; ICER, incremental cost-effectiveness ratio; IFN, interferon

Table 3. Issue 2 Generalisability of trial population to UK patients

Report section	2.3.1, 3.2.2, 4.2.2
Description of issue and why the EAG has identified it as important	The company used external literature sources to estimate baseline age and cirrhotic status in the model given that MYR 301 did not include patients from the UK. The company assumed that 60% of patients at baseline had CC, while the equivalent proportion in the MYR 301 trial was 47%. The company also assumed that patients were 35 years old at baseline, while this was 42 years in the trial. These assumptions have a considerable impact on the final ICER.
What alternative approach has the EAG suggested?	The EAG recommends that: 1) the company presents available data from literature during technical engagement to ascertain the typically presenting age and cirrhotic distribution of CHD patients in the UK; 2) the committee's clinical experts validate these assumptions.
What is the expected effect on the cost-effectiveness estimates?	Using the MYR 301 baseline age and cirrhosis distribution increases the final ICER (See Section 6.2 and 6.3). Furthermore, using the higher baseline age from the MYR 301 study also decreases the severity modifier weight from 1.2 (used in the company's base case) to 1 in the QALY shortfall estimation (see Section 7.1.1).
What additional evidence or analyses might help to resolve this key issue?	As above.

Abbreviations: CC, compensated cirrhosis; CHD, chronic hepatitis D; EAG, evidence review group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Table 4. Issue 3 Uncertainty in the extrapolations beyond the observed trial data

Report section	2.3.2, 3.4, 4.2.4, 4.2.10
Description of issue and why the EAG has identified it as important	The company extrapolated 48-week data from the trial for one cycle in the model (i.e., up to 72 weeks). The EAG considers the company's extrapolations of biochemical response to be flawed and considers that a more robust approach would have been to only include the 48-week trial data in the model. Given that patients from the MYR 301 study continue to be followed up and that data for 96 weeks of treatment are anticipated to become available in [redacted], the EAG notes that reliable observed data to populate the model for an additional 2 cycles will become available soon. Furthermore, the EAG notes that temporal data of response from MYR 301 show that some patients lost either biochemical or virological response between week 24 and week 48 while on bulevirtide treatment, that is, complete response was not sustained for everyone while on treatment.

	The optimal treatment duration with bulevirtide is also unknown. The company reports that treatment should be continued as long as associated with a clinical benefit and the SmPC states that discontinuation of treatment should be considered in case of loss of virological and biochemical response. In the MYR 301 trial, participants are scheduled to continued bulevirtide treatment up to 144 weeks. In the economic model, the company assumed that non-responders to treatment at week 48 discontinue treatment, however, the company did not provide a clear justification for this assumption and the EAG is unclear if 48 weeks was chosen due to this being the same data cut-off period available for MYR 301; or for any other reason such as the existing EASL guidelines, which strongly recommend treatment with PEG-IFN for at least 48 weeks in HDV-HBV coinfected patients with compensated liver disease, irrespective of on-treatment response pattern if well-tolerated. The EAG agrees with the company's assumption that partial responders who have not achieved a complete response continue treatment up to week 72, however, notes that in MYR 301, treatment is likely to have carried on for a longer period of time for these patients.
What alternative approach has the EAG suggested?	Duration of complete response and duration of treatment in the economic model will need careful re-assessment when the 96-week follow-up data are available for MYR 301. When more mature data are available, duration of treatment and time to response in the trial will need to be investigated, as it might be that, for example, non-responders at week 48 continued treatment and became responders later in the trial.
What is the expected effect on the cost-effectiveness estimates?	Not possible to predict the overall impact on the ICER – treatment costs would increase if non-responders stayed on treatment for longer than 48 weeks in the trial, however, partial responders might have also gained complete response by continuing treatment for longer than 48 weeks, therefore increasing the benefits associated with bulevirtide. For complete responders, if complete response was lost after 48 weeks, the benefits associated with bulevirtide would decrease, but so would costs.
What additional evidence or analyses might help to resolve this key issue?	Later data cut offs for MYR 301 may provide more robust data on patients who lose response while on treatment and data to inform the best timepoint for partial responders to come off treatment.

Abbreviations: EAG, evidence review group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Table 5. Issue 4 Modelling of HCC

Report section	4.2.4
Description of issue and why the EAG has identified it as important	Patients entering the HCC state in the model could only remain in the HCC state or transition to the LT state. Non-responders in the model have a probability of LT of 0.72% per 24-week cycle and a probability of 68% of remaining in the HCC state, with a 32% probability of death every cycle. The EAG is unclear on the clinical plausibility of this assumption, as the Barcelona Clinic Liver Cancer staging and treatment recommendations for HCC (as reported in TA551) suggest that patients, especially in the earlier stages of HCC, can be cured through other procedures such as resection or ablations. Furthermore, patients in the more advanced stages of cancer could transition to a progression-free state of the disease when treated.

	The EAG notes that the company's assumption, if not clinically plausible, is biased towards bulevirtide as a higher proportion of patients in the BSC arm of the model experience HCC and remain in that same state, experiencing very high costs and a low utility value.
What alternative approach has the EAG suggested?	The EAG recommends that the company validates this assumption at technical engagement and includes a scenario analysis in the model where a proportion of HCC patients can transition to a cure or a progression-free state of the disease.
What is the expected effect on the cost-effectiveness estimates?	If a proportion of HCC patients get cured without LT, it is likely that the cost-effectiveness of bulevirtide vs BSC will decrease, as BSC will become less burdensome. Nonetheless, the cost of treating HCC might counterbalance this effect.
What additional evidence or analyses might help to resolve this key issue?	As above.

Abbreviations: HCC, hepatocellular carcinoma; LT, liver transplant, EAG, evidence review group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

1.4 Summary of EAG's preferred assumptions and resulting ICER

The EAG's preferred assumptions are discussed throughout the report and consist of the following:

- Assuming that 48 weeks is the maximum timeframe for assessing final response to treatment, and treatment effectiveness is not extrapolated – Section 4.2.4.
- Using the observed trial data to estimate transition probabilities in the economic model for bulevirtide and best supportive care – Section 4.2.5.2.
- Estimation of the probability of hepatocellular carcinoma (HCC) from the F2-F4 states according to Romeo[2] and Kushner[3] -- Table 25, Section 4.2.5.3.1.
- Estimation of the probability of fibrosis progression from the F2-F4 states according to Romeo[2]- Section 4.2.5.3.1.
- Assuming that complete responders (CRs) have the same probability as partial responders (PRs), which is lower than the probability of non-responders (NRs), of developing HCC, instead of having a 0% probability of HCC.
- Using the 0.81 utility value to estimate the quality of life for NRs and PRs in the F-states, together with assuming a [redacted] utility value for CRs; and assuming that post-liver transplant (PLT) patients experience a [redacted] utility after transplant – Section 4.2.8.
- Adjusting utilities as per Ara and Brazier[1] – Section 4.2.8.
- Assuming that responders in the decompensated cirrhosis (DC) and HCC health states carry on with bulevirtide treatment – Section 4.2.10.

- Removing the F2 and F3 health state costs and including antiviral treatment costs for underlying HBV infection - Section 4.2.10.
- Removing the F4 health state costs and including antiviral treatment costs for underlying HBV infection - Section 4.2.10.

In addition to these assumptions, the EAG also produced an ICER with cumulative changes including the mean age and cirrhotic distribution at baseline to reflect the MYR 301 population (42 years and 47% of patients with compensated cirrhosis).

The cumulative EAG-preferred assumptions (Table 6), when external literature is used to estimate baseline characteristics, result in a final ICER of £48,518 per QALY gained; when MYR 301 is used to estimate baseline characteristics the ICER increases to £57,541.

While the EAG's clinical experts considered that the baseline characteristics included in the company's model were representative of the UK population, they noted that the baseline characteristics in the trial were not clinically implausible. Given the considerable impact that this assumption has on the final ICER, the EAG recommends that the committee seeks clinical expert opinion to assess the plausibility of the population characteristics in both scenarios. It is the EAG's opinion that the "true" ICER probably lies in between the two values.

Finally, the EAG notes that removing the utility gain associated with being a CR increases the EAG's ICER to £53,744 when external literature is used to estimate baseline characteristics, and to £64,765 when MYR 301 is used to estimate baseline characteristics.

Table 6. EAG's preferred model assumptions

Preferred assumption	Incremental costs	Incremental QALYs	ICER (change from company base case
Company base case (corrected)	[redacted]	[redacted]	£40,189
Assuming that 48 weeks is the maximum timeframe for assessing final response to treatment, and treatment effectiveness is not extrapolated	[redacted]	[redacted]	£40,851
Using the observed trial data to estimate TPs in the economic model for bulevirtide and BSC	[redacted]	[redacted]	£39,519
Estimation of the probability of HCC from the F2-F4 states according to Romeo[2] and Kushner[3]	[redacted]	[redacted]	£40,828
Estimation of the probability of fibrosis progression from the F2-F4 states according to Romeo[2]	[redacted]	[redacted]	£41,308

Assuming that CRs have the same probability as PRs (which is lower than the probability of NRs) of developing HCC, instead of having a 0% probability of HCC.	[redacted]	[redacted]	£42,909
Using the 0.81 utility value to estimate the quality of life for NRs and PRs in the F-states, together with assuming a [redacted] utility value for CRs; and assuming that PLT patients experience a [redacted] utility after transplant	[redacted]	[redacted]	£41,488
Adjusting utilities as per Ara and Brazier	[redacted]	[redacted]	£43,474
Assuming that responders in the HCC health states carry on with bulevirtide treatment	[redacted]	[redacted]	£40,199
Removing the F2 and F3 health state costs and including antiviral treatment costs for underlying HBV infection	[redacted]	[redacted]	£39,397
Removing the F4 health state costs and including antiviral treatment costs for underlying HBV infection	[redacted]	[redacted]	£39,105
The EAG changed the mean age and cirrhotic distribution at baseline to reflect the MYR 301 population (42 years and 47% of patients with compensated cirrhosis)	[redacted]	[redacted]	£43,594
EAG's assumptions combined when external literature is used to estimate baseline characteristics	[redacted]	[redacted]	£48,518
EAG's assumptions combined when MYR 301 is used to estimate baseline characteristics	[redacted]	[redacted]	£57,541

Abbreviations: EAG, evidence review group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

2 Introduction and background

2.1 Introduction

Herein is a critique of the evidence submitted to the Single Technology Appraisal (STA) in support of the clinical and cost-effectiveness of bulevirtide (brand name HEPCLUDEX®; Gilead Sciences, Inc.) in the treatment of chronic hepatitis D (CHD).

2.2 Background

Within section B.1 of the company submission (CS), the company provides an overview of:

- Bulevirtide, including its mechanism of action, dose and method of administration (CS, Section B.1.2);
- Hepatitis delta virus (HDV), including epidemiology and disease burden (CS, Section B.1.3).

Based on advice from its clinical experts, the Evidence Assessment Group (EAG) considers the CS to present an accurate overview of the epidemiology and aetiology of HDV, and the management of the disease.

Hepatitis delta, caused by HDV, is the most severe form of viral hepatitis. As it needs hepatitis B surface antigen (HBsAg) to complete its replication and transmission, this type of hepatitis only occurs in people also infected with hepatitis B virus (HBV)[4]. This can occur as a coinfection with HBV or as a superinfection in people with chronic hepatitis B (CHB) infection[5]. Clinical manifestations of chronic hepatitis vary, ranging from non-specific symptoms to rapidly progressing hepatitis; those with hepatitis delta may not present with any obvious symptoms until liver function is compromised, which means diagnosis is often by chance or once late complications have already occurred[6].

CHD is defined as an infection lasting at least 6 months. There is evidence that rates of disease progression, which includes liver-related events, cirrhosis, hepatocellular carcinoma (HCC) and death, are higher for those with CHD compared to patients with CHB monoinfection[7-9], and the EAG's clinical experts confirm that speed of progression in those with CHD can be much faster than those with only CHB or other types of liver disease such as alcoholic cirrhosis. Cirrhosis development and HCC are linked to increased morbidity and mortality and early treatment of CHD is therefore favourable as it could slow disease progression and the onset of these complications, which are difficult to treat and potentially life-threatening[10-13]. Although the EAG's clinical experts highlight that HCC in CHD can occur at any stage of fibrosis, it is noted that the risk increases considerably once cirrhosis develops. The EAG's clinical experts also note that disease regression (for example

moving from METAVIR fibrosis stage F3 to F2) is possible with treatment and can even occur for those with compensated cirrhosis (CC; METAVIR stage F4); those that are pre-cirrhotic or with early CC can return to normal while those with more advanced cirrhosis can improve. The EAG's clinical experts estimate that 50-75% of people with CC could regress once the virus was cleared, but that ~25% may still progress despite clearing the virus.

Hepatitis delta is recognised as an orphan disease by the European Medicines Agency (EMA), which indicates that the prevalence is below the threshold of 5 in 10,000 people.[14] The company estimates (see Figure 2 in the CS) that there are ~152 patients per year in the UK that are positive for HDV-ribonucleic acid (RNA) and would meet the criteria proposed by the company for treatment with bulevirtide (adults with CHD, METAVIR stage F2 or higher and either responding inadequately to, being contraindicated to or intolerant of interferon [IFN]-based therapy), though they acknowledge that their clinical experts indicate this may be an overestimate[15]. The EAG's clinical experts also note the small numbers of patients seen in UK practice from their experience.

2.2.1 Positioning of bulevirtide in the UK treatment pathway

The CS provides a reasonable overview of current service provision for the management of CHD, including detail of where the company proposes bulevirtide will fit in the treatment pathway.

Current treatment options for CHD are limited, with no approved treatment options specifically for CHD in the UK[16]. The company suggest in section B.1.3.2.1 of the CS that there is evidence that 10% of patients with CHD experience spontaneous recovery[4] and the EAG's clinical experts highlight that it is very rare for CHD to resolve spontaneously. Currently there is no full National Institute for Health and Care Excellence (NICE) guideline for the treatment of CHD, although there are some recommendations concerning drug treatments in people with HBV-HDV coinfection, including that those with coinfection and evidence of significant fibrosis (METAVIR fibrosis stage of at least F2 or Ishak stage of at least 3) should be offered a 48-week course of peginterferon alfa-2a (PEG-IFN), with treatment discontinued if there is no reduction in HDV RNA after 6 months to 1 year of treatment[17]. This use of PEG-IFN for the treatment of HDV is outside of its marketing authorisation[18] and NICE guidance (TA96)[19] is only available for the use of PEG-IFN in CHB monoinfection. The EAG's clinical experts agree that PEG-IFN is considered as an option for this group of patients in current practice; however, they also note that the limitations of this treatment mean it is only successful in ~20% of patients. The limitations include a wide range of side effects meaning it is not well tolerated, contraindications to the treatment, poor response rate and high relapse rate (~50%) once treatment is stopped if a response was initially obtained. The company also highlights this in the CS, estimating

the proportion obtaining a lasting benefit from PEG-IFN to be ~10% of those with CHD[9], and notes the effect this has on disease progression and health-related quality of life[9, 20-22].

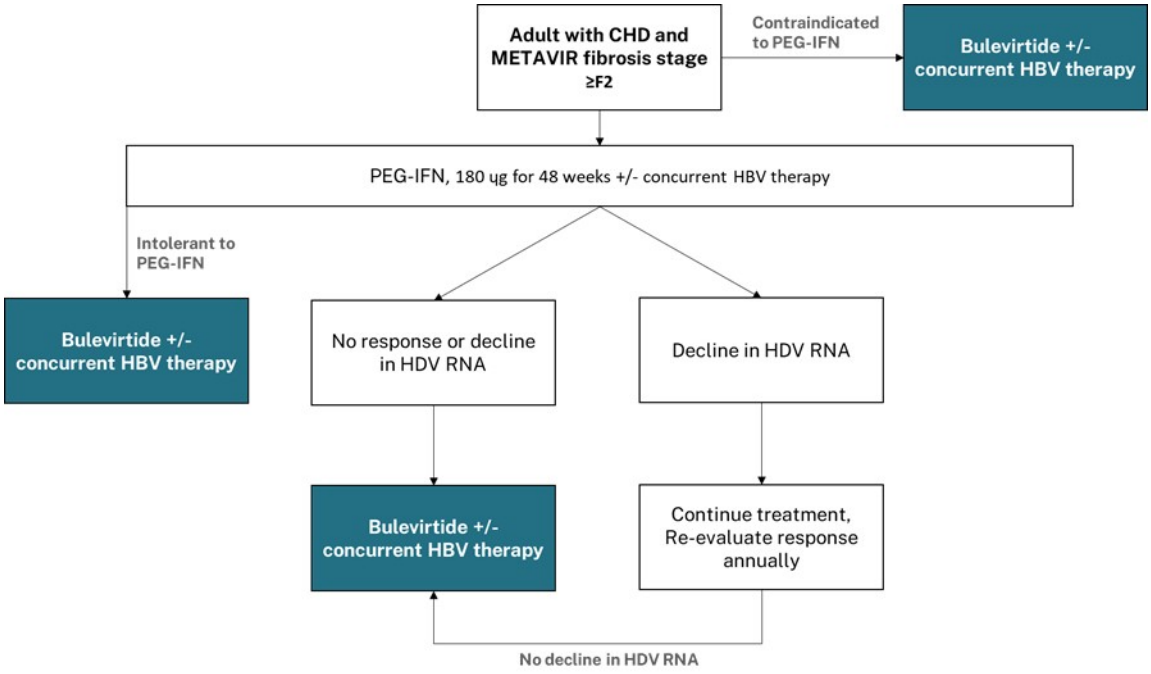
When patients have an inadequate response to PEG-IFN or when it is not an option, treatment options for CHD are limited to best supportive care (BSC), which involves symptomatic treatment and treatment of the underlying CHB where indicated. Treatments for underlying CHB include nucelos(t)ide analogues (NAs), such as tenofovir disoproxil and entecavir, which are used in UK practice. These are considered effective in those with CHB but have no meaningful effect on HDV RNA levels as these drugs do not inhibit the production of HBsAg required by HDV to replicate[20, 23], meaning HDV can still replicate. The EAG's clinical experts confirm that BSC and monitoring for need for liver transplant would be the only remaining option in those where PEG-IFN had failed or was not suitable. They highlight that a large proportion within this group may eventually need a liver transplant (at least 50% of those with HDV viraemia that progress to cirrhosis) and that a treatment to prevent progression to this stage would be beneficial for patients. The company concludes that there is, therefore, an unmet need for antiviral therapy to treat CHD in patients whose disease has not responded adequately to IFN-based therapy or for whom this is not an option due to intolerance of contraindication.

The company, therefore, has positioned bulevirtide for use in people with CHD with compensated liver disease and evidence of significant fibrosis (METAVIR stage of at least F2) whose disease has responded inadequately to or who are ineligible for IFN-based therapy due to intolerance or contraindication (see Figure 1 below). The EAG's clinical experts agree overall with this positioning but note that bulevirtide could also be considered as an alternative to PEG-IFN. However, they highlight that the limitations of PEG-IFN treatment mean that a substantial proportion of people with CHD, compensated liver disease and significant fibrosis are not offered treatment with PEG-IFN as they are either contraindicated or are unlikely to tolerate treatment. They also highlight differences in the treatment duration between these two drugs, as PEG-IFN treatment would be for a finite period whereas bulevirtide treatment is suppressive and likely to be taken for a long period of time.

The EAG's clinical experts anticipate that bulevirtide may be used alongside NAs to suppress HBV replication, but its concurrent use would likely depend on the levels of HBV for each person as well as how advanced liver disease was. NAs would help in preventing any disease activity from HBV, but would not have any effect on HDV levels. This is also highlighted in the CS, with the company's

proposed positioning of bulevirtide (see Figure 1 below) including options for concurrent or no concurrent treatment with HBV therapy while on bulevirtide treatment.

Figure 1. Proposed positioning of bulevirtide in the adult CHD treatment pathway (reproduced from Figure 6 of the CS)



CHD, chronic hepatitis delta; CS, company submission; HBV, hepatitis B virus; HDV, hepatitis delta virus; RNA, ribonucleic acid; PEG-IFN, peginterferon-alpha-2a.

2.3 Critique of the company's definition of the decision problem

The company provides a summary of the final scope issued by NICE[24], together with their rationale for any deviation from the final scope (Table 9). The company highlights that the main differences between the submission and the final scope are in terms of the population and the comparators given where the company have positioned bulevirtide in the treatment pathway for CHD. Key differences between the decision problem addressed in the CS and the scope are discussed in greater detail in the sections that follow but the EAG notes that the population in the CS is narrower than that specified by NICE and the population selected means that one of the comparators specified in the NICE scope is not deemed to be relevant.

Table 7. Summary of decision problem

	Final scope issued by NICE[24]	Decision problem addressed in the submission	Rationale if different from the scope	EAG comment
Population	Adults with CHD who have compensated liver disease.	Adults with CHD who have compensated liver disease, and evidence of significant fibrosis (METAVIR stage greater than or equal to F2), whose disease has responded inadequately to IFN-based therapy, or who are ineligible to receive IFN-based therapy due to intolerance or contraindication.	This positioning addresses the area of highest unmet need in the treatment of hepatitis delta. Where IFN-based therapy (PEG-IFN) is recommended by NICE clinical guideline CG165[17] but is not an option, either due to failure to respond, contraindication or intolerance, no alternative treatment options exist.	Overall, the EAG considers the narrower population specified in the decision problem to be reasonable. However, the EAG notes that the population in the key trial focused on in the CS (MYR 301) is not specific to this narrower population in terms of degree of fibrosis or prior IFN-based therapy, which may affect the generalisability of the trial results to the narrower population specified in the decision problem. See section 2.3.1 below for further discussion.
Intervention	Bulevirtide.	As per scope.	N/A	The intervention specified in the CS is bulevirtide, matching the final NICE scope. Bulevirtide is a chronic therapy with no stopping rules specified in it marketing authorisation (beyond futility). Therefore, there is uncertainty around when to discontinue bulevirtide treatment for non-responders, partial responders and complete responders. See section 2.3.2 below for further discussion.
Comparator(s)	• BSC • PEG-IFN	• BSC	Bulevirtide is the first and only approved treatment for CHD. Whilst it is acknowledged that IFN-based therapy is used off-label for some patients, in the absence of IFN-based therapy	Given the company positions bulevirtide for use in people that have had unsuccessful previous IFN-based treatment, or who were intolerant of or contraindicated to IFN-based treatment, PEG-IFN listed in the NICE final scope is not a relevant comparator in the CS.

			the only treatment option is BSC, which is generally defined as symptomatic treatment alongside treatment for the underlying HBV. In the population proposed, BSC is the appropriate comparator.	The EAG's clinical experts confirm that BSC in clinical practice usually involves symptomatic treatment with or without antiviral treatment for the underlying HBV infection, as well as monitoring for any liver complications. See section 2.3.3 below for further discussion.
Outcomes	The outcome measures to be considered include: • Virological response • Biochemical response • Sustained response • Development of resistance to treatment • Mortality • Adverse effects of treatment • Health-related quality of life	As per scope, except for sustained response and development of resistance to treatment. Some additional outcomes including liver stiffness and histological activity.	The outcome 'development of resistance to treatment' is not presented in the CS. This was not an endpoint in the pivotal MYR 301 trial and as such limited evidence exists to support this endpoint. The outcome 'sustained response' is not presented in the CS. It relates to continued virologic response post treatment completion. As bulevirtide is a chronic therapy with no licensed stopping rules (beyond futility) there is no possibility of 'sustained response'.	As liver-related complications such as HCC and death can take years to develop, surrogate outcomes were reported in the trials, which the EAG's clinical experts thought was reasonable. Most outcomes relevant to the NICE final scope have been provided by the company for the MYR 301 and MYR 202 trials. The EAG agrees that 'development of resistance to treatment' was not an endpoint assessed for all patients in the MYR 301 trial, but resistance analysis was performed for a subset of patients as confirmed at the clarification stage. The EAG agrees that the outcome of 'sustained response' after treatment discontinuation is of limited interest to this appraisal. However, data on sustained virological and/or biochemical response while on treatment is relevant to the decision problem. Data on the temporal pattern of participants' response rates were provided by the company at the clarification stage. The company estimated a health-related quality of life gain associated with complete response from the trial data, however, used external literature to estimate the health-related quality

				of life experienced by patients in all states of the model. The EAG disagrees with the company's approach and considers that the trial data should be used to estimate quality of life in all health states of the model. See section 4.2.8 and Section 6.2 for further discussion and the results of the EAG's analysis.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from NHS and Personal Social Services Perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The use of bulevirtide is conditional on the presence of HDV. The economic modelling should include costs associated with diagnostic testing for HDV in people with HBV	As per scope, apart from with regard to the final point about diagnostic testing for HDV in people with HBV.	NICE clinical guideline CG165 states that all adults who are HBsAg positive (i.e. have HBV infection) should be tested for HDV antibody (anti-HDV). A positive anti-HDV result must then be followed by a HDV RNA test, alongside liver fibrosis staging, in order to determine those patients currently infected with HDV who should be offered the 48-week course of PEG-IFN recommended in NICE clinical guideline CG165. As such, there are no additional diagnostic tests required for the population who are within the economic modelling presented herein.	The EAG agrees that NICE guideline CG165 for CHB recommends testing for anti-HDV for adults who are HBsAg positive, meaning there should be no change in the number of people being tested for HDV presence.

	who would not otherwise have been tested. A sensitivity analysis should be provided without the costs of the diagnostic test.			
Subgroups to be considered	If the evidence allows the following subgroups should be considered: • Severity of disease.	Severity of disease subgrouping suggested in scope performed as well as additional one related to prior IFN-based therpay. Severity of disease: • People with cirrhosis (METAVIR fibrosis stage F4). • People without cirrhosis (METAVIR fibrosis stage F0-F3). Prior IFN-based therapy status: • Prior treatment with IFN-based therapy • No prior treatment with IFN-based therapy	The company proposed analysing outcomes in patients with and without cirrhosis. The development of cirrhosis is associated with a substantial clinical burden, with people with cirrhosis having a higher probability of developing severe liver complications and lower overall survival compared to those without cirrhosis. An additional subgroup analysis for those with and without prior IFN-based treatment was also performed to see whether this had any effect on response to bulevirtide.	The subgroup suggested in the NICE final scope (severity of disease) was included in the CS. Severity subgroups were based on the presence or absence of cirrhosis, which the EAG's clinical experts agree is the most useful way of dividing patients based on disease severity. The EAG notes that this subgroup was prespecified and stratified for at randomisation in MYR 301. Although scenario analyses separately for cirrhotic and non-cirrhotic subgroups were requested by the EAG at the clarification stage, these were not provided by the company. See section 2.3.5 below for further discussion.
Other issues	N/A	N/A	N/A	The EAG noted that the longest time-point data is available for comes from the MYR 301 trial at 48 weeks, which is short considering bulevirtide would be required as a chronic treatment. See section 2.3.6 below for further discussion.

Abbreviations: anti-HDV; HDV antibody; BSC, best supportive care; CHB, chronic hepatitis B; CHD, chronic hepatitis D; CS, company submission; CSR, clinical study report; EAG, Evidence Assessment Group; HBsAg, Hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HDV, hepatitis delta virus; IFN, interferon; N/A, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PEG-IFN, peginterferon alfa-2a; RNA, ribonucleic acid.

2.3.1 Population

Clinical effectiveness data in the CS are derived from the MYR 301 and MYR 202 trials, comparing bulevirtide treatment with control groups receiving BSC (such as antiviral treatments for underlying HBV). The company primarily focuses on the MYR 301 trial, which was used to inform the economic model. Inclusion criteria for the two trials were similar, with the population being adults (18-65 years) with CHD (≥6 months prior to screening) with or without liver cirrhosis, excluding those with current or a history of decompensated liver disease (further details of trials are provided in Section 3.2).

The company specifies a population in the decision problem that is narrower than that in the NICE final scope[24], restricting it to adults with CHD with METAVIR fibrosis stage of at least F2 and who have experienced treatment failure with IFN-based treatment or who were contraindicated to or intolerant of IFN-based treatment rather than the broader group of adults with CHD and compensated liver disease. Overall, the EAG considers this narrower population in the decision problem to be reasonable given this represents a subset of patients covered in the conditional marketing authorisation with a particularly high unmet need in terms of treatment options. The EAG's clinical experts suggest that bulevirtide may be useful as an alternative to PEG-IFN rather than as an option when PEG-IFN is contraindicated, not tolerated or no response is achieved. However, the experts note that the company's positioning of bulevirtide is reasonable given that patients who fail on PEG-IFN therapy have no other treatment options and only a small proportion of patients with CHD will be suitable for or will achieve a sustained response with PEG-IFN. The EAG's clinical experts also note that bulevirtide and PEG-IFN differ in terms of treatment duration, as bulevirtide (if a response is achieved) will be continued for an indefinite period of time while PEG-IFN treatment is for a finite period.

Despite the company's positioning of bulevirtide for this specific population, the EAG notes that the population in the MYR 301 and MYR 202 trials is not specific to the population described by the company in the decision problem, as to be included there was no requirement for degree of fibrosis to be at least METAVIR stage F2 or for IFN-based therapy to have failed (or not used due to intolerance or contraindication):

- In both trials, liver biopsies were not a requirement for inclusion so METAVIR staging was not possible for a large proportion of patients. The EAG's clinical experts note that in

practice liver biopsies are always discussed with patients who are likely to have advanced disease, but that biopsy is often not favoured by patients due to their invasive nature;

- Both studies include people with any degree of fibrosis (from F0 to F4, not limited to METAVIR stage of at least F2) – of those in MYR 301 where METAVIR staging was performed at baseline [redacted], a substantial proportion in each group [redacted]. Due to concerns about this, the EAG asked for further data and a discussion of how this may impact the generalisability of the trial results to the population in the decision problem. Although no rationale was provided, the company concluded that the inclusion of patients with METAVIR stage lower than F2 would not affect the generalisability of the MYR 301 trial to the decision problem population. Additional data for response rates (virologic, biochemical and combined response) for each of the METAVIR fibrosis groups separately (F0 to F4) was requested at clarification but not provided by the company as they noted that small sample sizes within each stage at baseline and the large proportion with missing data for METAVIR staging at baseline and week 48 meant robust comparisons would be challenging. The EAG agrees that a robust analysis is unlikely to be possible but notes that the data by METAVIR staging could provide some indication of the generalisability of the full trial population to the population the company has focused on in the decision problem. Therefore, the EAG's concerns about the potential effect the inclusion of these patients may have on the results remains, particularly as the proportion differs between treatment groups.
- In response to a clarification request, the company clarified that cirrhosis status was based on the clinical judgement of investigators in MYR 301, including clinical, histological (e.g. METAVIR, Ishak and Knodell fibrosis scores) and other diagnostic measures such as FibroScan® (transient elastography measurements of liver stiffness as a surrogate measure of fibrosis). The EAG's clinical experts agree that transient elastography usually correlates relatively well with biopsy (which is required for histological assessment of fibrosis) in terms of confirming cirrhosis presence, although it may be less clear on distinguishing between other stages (for example between F2 and F3 or F1 and F2). They also note that there is still a role for biopsy in this population to accurately stage disease before starting a potentially long term treatment;
- The trials did not limit inclusion to those that had no response to, were intolerant of or were contraindicated to IFN-based treatment, with [redacted] of patients in the trials having

had prior treatment and it being unclear what proportion of the remaining patients were contraindicated; however, *post-hoc* subgroup analyses for those with prior IFN-based treatment were performed by the company.

Initially, the economic model only used outcome data for the subgroup with prior IFN-based treatment in the MYR 301 trial. However, at the clarification stage, the company revised the base case to include the full trial population as they agreed with the EAG that the full trial population may be more appropriate for the following reasons:

- the full trial population provides a larger sample size and includes patients who were intolerant of or for whom IFN-based therapy was contraindicated;
- the subgroup analysis results by prior IFN-based therapy does not indicate statistically significant differences in efficacy between the subgroups;
- and the trial was not stratified by prior IFN-based therapy at randomisation, meaning it was a *post-hoc* subgroup analysis that broke randomisation.

The EAG's clinical experts agree that using the full trial population is more appropriate in order to include those that were contraindicated to IFN-based treatment, rather than limiting to those that had been eligible for prior IFN-based therapy. However, in order to address the potential issue of generalisability of the full trial population to the decision problem population, which is limited to METAVIR stage F2 and above, the EAG propose a scenario analysis focusing on the cirrhotic subgroup of the trial. The cirrhotic subgroup should equate to a METAVIR stage of F4, in the economic model.

Some minor differences are noted between the trial populations and CHD patients in UK clinical practice, such as mean age being ~5 years higher in the trial and race distribution likely differing in UK practice. Overall, the EAG's clinical experts consider that the populations in the two trials are broadly representative of those seen in UK clinical practice with CHD. They also note that characteristics of patients are likely to differ across centres in the UK particularly given the small numbers of patients seen annually. External validity of included trials is further discussed in Section 3.2. As no UK centres are included in the MYR 301 trial, the company states that baseline characteristics from the trial are not generalisable to the UK population and baseline characteristics proposed for use in the model are obtained from other sources. While the EAG's clinical experts considered that the baseline characteristics included in the company's model were representative of

the UK population, they noted that the baseline characteristics in the trial were not clinically implausible.

The company's decision to focus on MYR 301 in terms of the economic model is deemed reasonable by the EAG given it provides data for a longer treatment duration than MYR 202 (48 weeks compared to 24 weeks, respectively). In addition, the control arm of MYR 301 may be more representative of clinical practice in the UK as various HBV antiviral treatments were an option (tenofovir and entecavir are options used in UK clinical practice) but not a requirement, whereas in MYR 202 all patients received tenofovir in the control group.

In summary, the EAG's clinical experts consider the company's proposed positioning and target population for bulevirtide to be reasonable given it is a subgroup with a particularly high unmet need and that the data from the key trials, particularly MYR 301, are likely to be relevant for UK patients. However, the EAG has some concerns about the generalisability of the full trial population to the population the company specifies in the decision problem.

2.3.2 Intervention

The intervention covered in the CS is bulevirtide, which matches the NICE final scope[24]. A summary of bulevirtide is provided in Table 2 of the CS. Bulevirtide is the only approved treatment for CHD in Europe. A conditional marketing authorisation (reliance procedure) for bulevirtide (2 mg given subcutaneously once daily) was received from the Medicines and Healthcare products Regulatory Agency (MHRA) on 16 November 2021[25] under the brand name HEPCLUDEX®.

The marketing authorisation is for CHD infection in plasma (or serum) HDV-positive adult patients with compensated liver disease. Bulevirtide is intended for subcutaneous injection into the upper thigh or abdomen as a single 2 mg dose daily, with patients able to self-administer the product following appropriate training. Bulevirtide is recommended either as monotherapy or alongside an NA for treatment of the underlying HBV infection, which the EAG's clinical experts note includes tenofovir or entecavir in UK clinical practice.

The company reports that the optimal treatment duration with bulevirtide is unknown and that treatment should be continued as long as associated with clinical benefit, with the Summary of Product Characteristics (SmPC; Appendix C of the CS) stating that discontinuation of treatment should be considered in case of sustained (6 months) HBsAg seroconversion or loss of virological and biochemical response. There are no stopping rules reported in the SmPC other than lack of or loss of

efficacy, although it does highlight the lack of safety, efficacy and pharmacokinetics data in those with decompensated liver disease and advises against its use in this population. Treatment regimens used in the MYR 301 and MYR 202 trials were in line with those described in the SmPC and are discussed in Section 3.2. However, in MYR 301 participants are scheduled to continued bulevirtide treatment up to 144 weeks. The EAG assumes that treatment is continued for the full trial duration irrespective of response, i.e. also for non-responders, partial responders and complete responders who lose either their virological or biochemical response whilst on treatment. However, in the economic model the company assumes that patients who haven't responded by week 48 will discontinue treatment at that timepoint, patients with a partial response are assumed to discontinue treatment at 72 weeks and complete responders are assumed to continue treatment indefinitely. The EAG's clinical experts states that patients will be monitored on treatment with response likely to be assessed after 12 weeks and 24 weeks of treatment, but that it is reasonable to make a final judgement around treatment discontinuations for non-responders at 48 weeks. It is less clear for how long to continue treatment for patients who achieve a virological response but not a biochemical response, but it may be reasonable to assess whether to continue treatment of partial responders at 72 weeks.

At the clarification stage the company noted that as decompensated liver disease and previous or current neoplasms (including HCC) were exclusion criteria for previous trials (MYR 202 and MYR 203) and the MYR 301 study, there are no data for safety, pharmacokinetics or efficacy in these groups, which is why bulevirtide is discontinued for these groups in the economic model. The EAG's clinical experts advise that if bulevirtide treatment is effective in a patient, treatment with bulevirtide would likely need to be continued for a long time to suppress HDV. This differs from PEG-IFN treatment which in clinical practice is used for a finite period of time.

2.3.3 Comparators

The comparators specified in the NICE final scope[24] include BSC and PEG-IFN. Due to the differences in the proposed population between the NICE final scope and the CS, PEG-IFN is not considered a relevant comparator to bulevirtide; the company limits the population to those that have failed prior IFN-based treatment or for whom it is not tolerated or is contraindicated.

The EAG's clinical experts agree with the NICE final scope, that there could be a place for bulevirtide as an alternative to PEG-IFN rather than as a treatment to use after PEG-IFN has failed or been deemed not suitable. However, overall the EAG's experts think the company's positioning is

reasonable given the proposed population is a group with no other treatment options and only a small proportion of patients will be suitable for or will achieve a sustained response with PEG-IFN.

BSC was the comparator used in the MYR 301 and MYR 202 trials, although this differed slightly between the two trials. The EAG's clinical experts confirmed that BSC in clinical practice usually involves symptomatic treatment with or without antiviral treatment for the underlying HBV infection, as well as monitoring for any liver complications. The EAG notes that the comparator arm in the MYR 301 trial may be more relevant to UK clinical practice, as it includes the option for antiviral treatment (not a requirement for all which is the case in the MYR 202 trial) and includes antiviral treatments other than tenofovir; the comparator arm in the MYR 202 trial required all patients to be taking tenofovir, whereas in UK practice tenofovir and entecavir are options.

2.3.4 Outcomes

Most outcomes relevant to the NICE final scope[24] are provided in the CS for the MYR 301 and MYR 202 trials.

The company states that 'development of resistance to treatment' could not be reported given it was not an end-point in the MYR 301 trial; the EAG agrees that this was not an endpoint assessed for all patients in the MYR 301 trial, but the company confirmed at the clarification stage that resistance analysis was performed for a subset of patients with virological breakthrough (two consecutive increases in HDV RNA 1 $\log_{10}$ IU/ml from nadir or two consecutive HDV RNA values ≥ lower limit of detection [LLOD] if previously <LLOD) or HDV RNA decline <1 $\log_{10}$ IU/ml (non-responders) at week 48.

Similarly, no data are presented in the CS for 'sustained response' after treatment discontinuation. The EAG agrees with the company that as bulevirtide is designed as a chronic therapy this outcome is of limited interest for this appraisal, but notes that 48-week results for the MYR 202 trial do provide some evidence for this (Section B.2.6.2 of the CS), as in this trial all patients stopped treatment at 24 weeks, as per the trial design, which allows the effects on efficacy once bulevirtide is stopped to be observed. In addition, the EAG notes that the data on virological and biochemical response from MYR 301 indicate that response may not be maintained during treatment for all patients. At the clarification stage further data showing the number of patients moving between response states from week 24 to week 48 (response to clarification question A3) were provided.

The company highlights that the aim of CHD treatment is to prevent the development of complications of liver disease, such as HCC and death, but that it is not feasible to assess these outcomes directly in clinical trials given the large sample size and prolonged follow-up period that would be required. For this reason, surrogate markers included in the MYR 301 and MYR 202 trials (including virological and/or biochemical response to treatment) are deemed appropriate by the company, as there is evidence linking these outcomes with disease progression outcomes further down the line (Section B.1.3.2.2 in CS). The EAG's clinical experts agree that these surrogate outcomes are relevant and useful for predicting disease progression outcomes (which can take years to develop) in people with HBV or hepatitis C virus (HCV) and it would be reasonable to use the same surrogates for HDV.

2.3.5 Subgroups

The NICE final scope[24] specified subgroups to be considered based on the severity of the disease, which has been provided in the CS. The company splits subgroups based on the presence or absence of cirrhosis, which the EAG's clinical experts agree is reasonable as this is where differences in outcomes would most likely occur. In addition, distinguishing between earlier fibrosis stages (for example F2 and F3) can be less clear cut. The subgroup analysis based on presence or absence of cirrhosis was prespecified in the trials and randomisation was stratified for this factor. Despite being stratified by cirrhosis status at baseline, the EAG note that separate data for those with and without cirrhosis were not included in the economic model, although this was requested by the EAG as scenario analyses at the clarification stage. Although the company considered the sample sizes in MYR 301 for the cirrhotic and non-cirrhotic subgroups too small to establish meaningful groups to estimate transition probabilities for use within the economic model, the EAG note that the initial model base case submitted by the company was limited to a similarly small group of those that had prior IFN-based therapy. The EAG, therefore, maintains that a scenario analysis testing the difference in model output in these subgroups is important. At the clarification stage the EAG also requested data for additional outcomes for each of these two subgroups as well as baseline characteristics, which were provided by the company.

An additional subgroup analysis based on prior or no prior IFN-based treatment was also included in the CS, which was not outlined in the NICE final scope.[24] Although the original economic model base case used data specifically from the IFN-experienced subgroup of the MYR 301 trial, at the clarification stage the company agreed with the EAG that it would be more appropriate to use more

robust evidence from the full trial population. Reasons that the full trial population was considered more robust are discussed in Section 2.3.1 above.

2.3.6 Other issues

Considering bulevirtide is described by the company as a chronic treatment with no stopping rules other than futility (Table 9) presented within the SmPC, the EAG notes that the 48-week treatment period in MYR 301 is quite short and data beyond this time-point to determine whether those achieving a response with bulevirtide sustain this longer term would be useful. Although the EAG is aware that this trial is ongoing and the bulevirtide treatment groups are scheduled to continue treatment up to 144 weeks, the plan for the comparator arm after 48 weeks is to start treatment with bulevirtide 10 mg (Figure 7 of the CS), meaning the comparator after the 48-week time-point will no longer be BSC and will not be relevant to the decision problem. However, the EAG's clinical experts note that based on the mechanism of action for bulevirtide, they do not expect resistance to bulevirtide to develop. Despite this, longer term comparative data from trials to confirm this would be useful.

3 Clinical effectiveness

3.1 Critique of the methods review

The company conducted a systematic literature review (SLR) to identify randomised controlled trials (RCTs) reporting data on the efficacy, safety and tolerability of pharmacological treatments for adults with chronic hepatitis delta (CHD) who have compensated liver disease. An original SLR was conducted in October 2020, which was updated twice, once in April 2021 and once in December 2021. The inclusion and exclusion criteria of the SLR matched the population, interventions, comparators and outcomes specified in the final scope issued by the National Institute for Health and Care Excellence (NICE)[24], and not the narrower population focused on in the company submission (CS). The company presents the methods and results of the clinical SLR in Appendix D of the CS, and the External Assessment Group's (EAG's) critique of them is presented in Table 1. As the company used the same SLR searches to identify cost-effectiveness evidence, information from Appendix G of the CS has been used to supplement information from Appendix D during the EAG's critique.

In total, 19 studies (63 records) were included from the clinical SLR, with five studies (15 records) being identified as providing direct clinical evidence for the efficacy and safety of bulevirtide in adults with CHD (Table 3, Section B.2.2). However, as the CS addressed a narrower population than the NICE final scope, three studies were excluded because they compared bulevirtide with interferon (IFN)-based therapies. Two studies were ultimately deemed relevant to the decision problem addressed in the CS, MYR 301[26] and MYR 202[27], which each contained a bulevirtide 2 mg arm and best supportive care arm for at least some duration of follow-up.

MYR 301 is an ongoing, Phase III, multicentre, open-label, randomised trial and was the key trial used in support of the submission. MYR 301 evaluates the clinical efficacy and safety of bulevirtide 2 mg and bulevirtide 10 mg, compared to 48-week delayed treatment of bulevirtide 10 mg, over a period of 144 weeks. At the time of the CS, MYR 301 data were available up to Week 48 of the trial.

MYR 202 also provided some supporting data in the submission. MYR 202 was a Phase II, multicentre, open-label, randomised trial and evaluated the efficacy and safety of bulevirtide 2 mg + tenofovir disoproxil fumarate (TDF), bulevirtide 5 mg + TDF, bulevirtide 10 mg + TDF and TDF alone over a 24-week period, after which all participants were treated with TDF alone for a further 24 weeks.

Only the data from the bulevirtide 2 mg arms and the delayed treatment arm (MYR 301) or TDF alone arm (MYR 202) are focused on in the CS, as bulevirtide 2 mg is the dosage under consideration. Overall, the EAG considers the company's SLR and selection criteria to be of satisfactory quality and likely to have retrieved all studies relevant to the decision problem outlined in the company submission.

Table 8. Summary of EAG's critique of the methods implemented by the company to identify evidence relevant to the decision problem

Systematic review step	Section of CS in which methods are reported	EAG's assessment of robustness of methods
Data sources	Appendix D, Section D1.1 (Table 75). Appendix G	**The EAG considers the sources and dates searched to be comprehensive.** Databases searched: • Embase; MEDLINE; PubMed-not-MEDLINE; CENTRAL; CDSR; HTA Database; NHS EED Registries: • WHO ICTRP; ClinicalTrails.gov; EU-CTR; ICTRP; PharmNet.Bund HTA Bodies: • NICE; SMC; IQWiG; G-BA; Institute for Clinical and Economic Review; PBAC; CADTH; HAS Conference proceedings: • AASLD; EASL; International Liver Congress; ECCMID; ISPOR; American Transplant Congress Other Grey Literature: • CEA Registry; EuroQol Group; The international HTA database of the International Network of Agencies for Health Technology Assessment; Reference list searches of relevant SLRs, (N)Mas, economic evaluations and HTA submissions The original search was conducted in October 2020, which were updated in April 2021 and December 2021. Conferences were searched between 2018 and 2021.
Search strategies	Appendix D, Section D1.1	**The EAG is satisfied that the company's searches have identified all evidence relevant to the decision problem.** The search strategies for the literature review used free-text keywords and medical subject headings to identify articles reporting on CHD or HDV. The search was broad and did not include terms for interventions or outcomes, meaning that all records reporting on CHD patients were likely to have been captured.
Inclusion criteria	B.2.2 & Appendix D, Section D1.1 (Table 76)	**The EAG considers it likely that no relevant evidence was excluded based on the eligibility criteria used.** The inclusion and exclusion criteria matched the target population, intervention, comparators, outcomes and study designs defined by NICE in

		the final scope. Records were limited to English language studies or studies with an English language abstract. A reference list of all included records, and records excluded at full text review, was provided in Appendix D, Section D1.1.
Screening	B.2.2 & Appendix D, Section D1.1 (Figure 21)	**The EAG considers the reporting of methods for screening to be adequate.** Records were dual screened at both the abstract and full text review stage. The results of the screening process were reported both within text (Appendix D, Section D1.1) and in a PRISMA diagram (Appendix D, Figure 21). The PRISMA diagram was only presented as an overall figure upon completion of the second SLR update, and it is not reported how many records were included from each of the original SLR and two updates.
Data extraction	NR/Appendix G	**Details on how data were extracted were not reported for the clinical SLR**. Only two studies were ultimately included in the CS from the clinical SLR. How data were extracted from records relating to these studies was not reported, but both studies were sponsored by the company. It is possible that all data presented in the CS was on file, and not extracted from publications identified in the SLR.
Tool for quality assessment of included study or studies	Appendix D, Section D1.3 (Table 80 and Table 81)	**The EAG agrees with the company's choice of quality assessment tool.** The company used an appropriate method[28] to assess the quality of the two included studies and provided detailed justification for each of the quality assessment answers. The EAG's assessment of MYR 301 is presented in Section 3.2.

Abbreviations: AASLD: American Association for the Study of Liver Diseases; CADTH: Canadian Agency for Drugs and Technologies in Health; CEA: Cost-Effectiveness Analysis; CDSR: Cochrane Database of Systematic Reviews; CS: company submission; EASL: European Association for the Study of Liver Diseases; ECCMID: European Congress for Clinical Microbiology and Infectious Diseases; EAG: evidence review group; EU-CTR: EU Clinical Trials Register; G-BA: The Federal Joint Committee; HAS: Haute Autorité de Santé; HTA: Health technology assessment; IQWiG: German Institute for Quality and Efficiency in Health Care; ISPOR: International Society for Pharmacoeconomics and Outcomes Research; NHS EED: National Healthcare Service Economic Evaluation Database; NICE: National Institute of Health and Care Excellence; NMA: network meta-analysis; PBAC: Pharmaceutical Benefits Advisory Committee; SLR: systematic literature review; SMC: Scottish Medicines Consortium; WHO ICTRP: World Health Organisation International Clinical Trials Registry Platform

3.2 Critique of trial of the technology of interest

In this section, the EAG critiques the MYR 301 trial as the key trial in the CS. MYR 301 was the only trial that informed the company's economic model, and the details of MYR 301's methods are presented in B.2.3.1 in the CS. The EAG's critique of the design, conduct and internal validity of MYR 301 is presented in Table 2. The critique focuses on the comparison between the delayed treatment arm and the bulevirtide 2 mg arm, as this is the dosage under consideration.

The EAG does not focus on MYR 202 in this critique and agrees with the company that it is appropriate to focus on MYR 301 in this appraisal. MYR 301 provides data up to Week 48 and from a larger sample size than MYR 202, which only provided comparative data up-to Week 24. MYR 202

was also at risk of bias from the non-random assignment of [redacted] to the bulevirtide arms only based on their consent to participate in a pharmokinetic sub-study[29], as well as a large imbalance in participants' baseline ALT levels between the bulevirtide 2 mg + TDF arm compared to the TDF alone arm (bulevirtide 2 mg + TDF, mean [SD], U/L: [redacted]; TDF alone: [redacted]). While the company did present a direct meta-analysis combining the clinical outcomes at Week 48 of MYR 301 and MYR 202 (Section B.2.8 of the CS), the EAG considers this meta-analysis inappropriate: participants in the bulevirtide 2 mg arm of MYR 202 only received bulevirtide up to Week 24, and then TDF alone up to Week 48, and therefore these participants are not comparable to those who had been treated with bulevirtide 2 mg for the full 48 weeks in MYR 301.

Table 9. A summary of the EAG's critique of the design, conduct and analysis of MYR 301

Aspect of trial design or conduct	Section of CS in which information is reported	EAG's critique
Randomisation	B.2.3, CSR	**Appropriate** Participants were randomised 1:1:1 to delayed treatment, bulevirtide 2 mg and bulevirtide 10 mg using an electronic randomisation system. Randomisation was stratified based on liver cirrhosis status.
Concealment of treatment allocation	NA	**The details of treatment concealment were not reported in the submission or CSR**
Eligibility criteria	B.2.3	**Appropriate** The EAG considers the eligibility criteria of MYR 301 to be appropriate in identifying adult patients with CHD and compensated liver disease. CHD patients were identified based on PCR and antibody tests, and appropriate exclusion criteria were used to exclude patients with decompensated liver disease. While MYR 301 only included adults aged 18-65 years, the EAG's clinical experts agreed this accurately reflects the patient landscape in the UK.
Blinding	B.2.3	**Risk of bias** MYR 301 was an open label study and therefore is susceptible to a range of biases because of a lack of blinding. Biases at the time of measurement are more likely for the patient reported HRQoL outcomes, adverse event reporting and treatment adherence rather than the key clinical outcomes, which were more objective measures. However, it is not possible to rule out that participants' behaviour and lifestyle choices may have differed between those who knew they were being treated with bulevirtide and those who were not, which could affect ALT levels.
Baseline characteristics	B.2.3.1.7, Table 9	**Participant baseline characteristics were largely balanced between the bulevirtide 2 mg and delayed treatment arms in the ITT population.**

		Slight imbalances were present in gender, HBV genotype and HBV DNA levels, but the EAG's clinical experts suggested that these are unlikely to meaningfully affect outcomes, with the possible exception of gender.
Dropouts	Appendix D1.2, Figure 22	[redacted]
Statistical analysis		
Sample size and power	B.2.4.1.3, CSR	**Some concerns** The company determined a target sample size of 50 participants per treatment arm to provide 95.6% power detect differences of between an assumed 45% response rate in the bulevirtide arms and an assumed 8% response rate in delayed treatment. The expected difference in response rate were based on the results of MYR 202. However, the observed response rates of MYR 202 at Week 24 were 21.4%, 21.8% and 36.7% for bulevirtide 2 mg, 5 mg and 10 mg, respectively, and the company did not justify their target effect size clinically. Hence, MYR 301 may have been underpowered to detect some clinical meaningful differences in response rates between bulevirtide 2 mg and delayed treatment at Week 48.
Handling of missing data	B.2.4.1.3	The company used last observation carried forward for data missing as a result of COVID-19 and used non-responder imputation for other missingness in response rate outcomes. The EAG does not consider LOCF to be appropriate, however, the overall rate of missingness because of COVID-19 was low (n=1 visits missed at both Week 24 and Week 48 for both delayed treatment and bulevirtide 2 mg).
Outcome assessment	B.2.3.1.6, CSR 7.3.6, Table 3, 7.4.1, CSR 7.7.2	**Appropriate** The clinical measurement of HDV RNA was conducted by central laboratories that were blinded to treatment allocation. ALT measurements used in the efficacy analysis came from locally conducted and assessed safety samples as a result of the instability of samples sent to the central laboratory. Two different thresholds were used to define ALT normalisation, with a stricter threshold being applied in Russian centres than all others. Despite this, the EAG considers the outcome assessment to be appropriate and unlikely to bias the results in favour of bulevirtide.
Analysis for estimate of effect	B.2.3.1.7, B.2.4.1	**Appropriate** The company performed all efficacy analyses on the ITT population, the full analysis set in the CS (Table 8). The analyses for the primary and key secondary endpoints (undetectable HDV RNA and ALT normalisation) used Fisher's exact tests to compare the proportion of responders and non-responders with an overall α=0.05. All tests were two-sided. While using continuous outcomes instead of responder analysis may have increased the statistical power of the analyses to detect decreases in HDV RNA or ALT levels, the EAG deems the responder analyses and estimation procedures to be appropriate

Abbreviations: ALT: alanine aminotransferase; CHD: chronic hepatitis delta; CSR: clinical study report; EAG: evidence review group; HDV: hepatitis delta virus; HRQoL: health-related quality of life; ITT: intention-to-treat; NICE: National Institute of Health and Care Excellence; PCR: polymerase chain reaction

3.2.1 Eligibility criteria

The eligibility criteria of MYR 301 (Section B.2.3, CS) were in-line with the population specified in the NICE final scope, however the company focuses on a narrower population in the economic model, as detailed in Section 2.3.1 and Section 4.2.2.

The EAG notes that an eligibility criterion of MYR 301 was having alanine aminotransferase (ALT) levels above the upper limit of normal (ULN). ALT normalisation, i.e., an ALT level falling below the ULN, was then measured as an outcome variable. However, using a variable that participants were selected for at baseline as an outcome measure will lead to regression to the mean.[30, 31] This may cause a trial-wide overestimation of the rate of ALT normalisation. In-line with this assertion, [redacted] (CSR Table 14.2.3.3-17).

The EAG assessed all other eligibility criteria to be appropriate.

3.2.2 Participant characteristics

In general, participant characteristics were well-balanced between the delayed treatment arm and the bulevirtide 2 mg arm in MYR 301, including for the key ALT and HDV RNA outcome variables, and exposure to previous IFN-based therapy. Randomisation was also stratified by cirrhosis status. A summary of these key baseline characteristics is presented in Table 3, and other baseline characteristics and demographic variables are presented in Table 12 of the CS.

Table 10. Key balanced participant baseline characteristics in MYR 301 (FAS)

Measure	Delayed Treatment (n=51)	Bulevirtide 2 mg (n=49)
Cirrhosis Status, n (%)		
Present	[redacted]	[redacted]
Absent	[redacted]	[redacted]
ALT (U/L), mean (SD)	[redacted]	[redacted]
HDV RNA (log_{10} IU/mL), mean (SD)	[redacted]	[redacted]

Prior INF-based therapy, n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]

Abbreviations: ALT: alanine aminotransferase; FAS: full analysis set; HDV: hepatitis delta virus; INF: interferon
Sources: CS Table 9; CSR Table 10

However, there were slight imbalances in the sex, HBV genotype and baseline HBV DNA levels of participants enrolled into the delayed treatment arm and bulevirtide 2 mg arm. The EAG's clinical experts suggested that HBV genotype and baseline HBV DNA levels are unlikely to affect the trial outcomes, but sex might. Male participants comprised a larger proportion of participants in the bulevirtide 2 mg arm (61.2%) than the delayed treatment arm (51.0%, CS Table 9, B.2.3.1.7).

The EAG considers two other baseline characterises to be important when interpreting the results of MYR 301: the location of participants across arms and the METAVIR fibrosis stage of participants at baseline.

Different thresholds were used in different countries to define the ULN for ALT response (Section 3.2.3):

- ULN for Russian centres: ≤ 31 U/L for females and ≤ 41 U/L for males;
- ULN for all other centres: ≤ 34 U/L for females and ≤ 49 U/L for males.

However, the EAG considers this unlikely to impact on the results of the trial as similar proportions of patients were from the different countries across the treatment arms of the trial.

The CS focused on adults with "significant evidence of fibrosis", defined by the company as a METAVIR fibrosis stage of F2 or greater. At baseline, METAVIR fibrosis staging data were available for [redacted] of participants across the delayed treatment and bulevirtide 2 mg arm. Baseline METAVIR data were missing for [redacted] of participants without cirrhosis and for [redacted] of participants with cirrhosis. Data were missing for participants who were ineligible for biopsy or who did not consent to biopsy.

Among the participants with METAVIR data available, a relatively large imbalance in METAVIR fibrosis staging is apparent between the bulevirtide 2 mg arm and the delayed treatment arm:

[redacted] of participants with METAVIR data available had a baseline METAVIR fibrosis stage of F0 or F1 in the bulevirtide 2 mg arm [redacted], whereas [redacted] of participants with METAVIR data available had a baseline METAVIR fibrosis stage of F0 or F1 in the delayed treatment arm ([redacted]). The distribution of baseline METAVIR fibrosis scores are presented in Table 4. The EAG notes two concerns about the baseline METAVIR fibrosis scores of MYR 301 participants. First, non-cirrhotic participants in the delayed treatment arm had a greater degree of fibrosis than participants in the bulevirtide 2 mg arm, which may have made it more difficult for delayed treatment participants to achieve biochemical response. Second, the large proportion of participants without F2 or greater METAVIR fibrosis score limits the generalisability of the MYR 301 participants to the company's proposed population: the clinical efficacy data from MYR 301 contains data from participants with less fibrosis – and potentially a larger probability of response.

Table 11. METAVIR fibrosis scores at baseline of MYR 301 participants

Arn	METAVIR fibrosis score at baseline					
	F0	F1	F2	F3	F4	Missing
Non-cirrhotic participants						
Delayed Treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bulevirtide 2 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cirrhotic participants						
Delayed Treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bulevirtide 2 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Overall						
Delayed Treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bulevirtide 2 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Sources: CSR, Ad Hoc Tables 10979.1, 10979.4 and 10979.5

Finally, the company did not deem the baseline characteristics of MYR 301 to be generalisable to UK practice (section B.3.3.1), with participating centres in MYR 301 only being in Russia, Germany, Italy and Sweden (B.2.3.1.1). Instead, the company used external data in the model, which are described in Section 4.2.2. The EAG's clinical experts judged the model inputs used by the company to be reasonable, but also noted that the MYR 301 population was also generally comparable to UK participants likely to be eligible for bulevirtide treatment

3.2.3 Outcome assessment

The EAG considers the assessment of the virologic and biochemical responses, and hence complete response, to be adequate. HDV RNA was measured at a blinded central laboratory. Virological response was defined as undetectable HDV RNA or a decrease from baseline in HDV RNA by $\geq 2\log_{10}$ IU/mL.

To assess ALT levels, two samples of ALT were collected at each visit: one for the efficacy analysis (blinded central laboratory) and one for the safety analysis (local laboratory). However, because of the instability of the sample sent to the blinded central laboratory, the sample from the safety analysis was used for the efficacy analysis. As the measurement of serum ALT is a relatively objective measure, the EAG deemed the use of the safety data appropriate for the efficacy analysis.

Different thresholds were used to define the ULN for ALT response in the trial:

- ULN for Russian centres: ≤ 31 U/L for females and ≤ 41 U/L for males;
- ULN for all other centres: ≤ 34 U/L for females and ≤ 49 U/L for males.

The EAG's clinical experts confirm that there is large variability between labs and between countries in ALT assessments and a lack of consensus around what thresholds to use to define ALT normalisation. The EAG notes that while this is unlikely to bias results in favour of bulevirtide, it may make the interpretation of the results more difficult to apply to UK practice.

3.3 Critique of the clinical effectiveness analysis

3.3.1 Combined, virologic and biochemical responses

The primary outcome in MYR 301 was achieving a combined response at Week 48, i.e., fulfilling the criteria for both virologic and biochemical response:

- Virologic response: undetectable HDV RNA or decrease in HDV RNA levels by ≥2log10 IU/mL from baseline;
- Biochemical response: ALT normalisation, defined as ALT levels within the ULN. The ULN was ≤ 31 U/L for females and ≤ 41 U/L for males at Russian centres, and ≤ 34 U/L for females and ≤ 49 U/L for males at all other centres.

The proportion of participants in each arm achieving virologic, biochemical and combined responses at Week 24 and Week 48 are presented in Table 5, and in B.2.6.1 of the CS. While the company presents analysis on both the ITT population (main analysis) and per-protocol population (supportive analysis), the EAG focuses only on the ITT analysis. The results of the per-protocol analysis were consistent with the ITT analysis throughout.

In total, [redacted] achieved the combined response at Week 48 in the bulevirtide 2 mg arm, compared to [redacted] in the delayed treatment arm. The EAG agrees this is a large and clear clinical benefit of bulevirtide over delayed treatment, i.e., current best supportive care, at Week 48. This benefit was also visible in both individual components of the combined response: [redacted] had a HDV RNA decrease by ≥2-log10 IU/mL or undetectable HDV RNA at Week 48 in the bulevirtide 2 mg arm, compared to [redacted] in the delayed treatment arm. Similarly, [redacted] achieved ALT normalisation at Week 48 the bulevirtide 2 mg arm, compared to [redacted] in the delayed treatment arm.

Table 12. Combined, virologic and biochemical response at Weeks 24 and 48 in MYR 301

Response	Timepoint	
	Week 24	Week 48
HDV RNA decrease by ≥2log$_{10}$ IU/mL or undetectable HDV RNA		
Delayed treatment (n=51), n (%)	[redacted]	[redacted]
Bulevirtide 2 mg (n=49), n (%)	[redacted]	[redacted]
ALT levels within the upper level of normal		

Delayed treatment (n=51), n (%)	[redacted]	[redacted]
Bulevirtide 2 mg (n=49), n (%)	[redacted]	[redacted]
Combined response		
Delayed treatment (n=51), n (%)	[redacted]	[redacted]
Bulevirtide 2 mg (n=49), n (%)	[redacted]	[redacted]

Source: CS B.2.6.1, additional data provided by company

Abbreviations: ALT: alanine aminotransferase; HDV: hepatitis delta virus

The clinical benefit of bulevirtide 2 mg over delayed treatment is also apparent when considering the change from baseline in HDV RNA and ALT levels, which are presented in Table 6. Participants in the bulevirtide 2 mg arm experienced a larger mean decrease from baseline in HDV RNA levels by Week 48 than participants in the delayed treatment arm (bulevirtide 2 mg: [redacted] $\log_{10}$ IU/L reduction; delayed treatment: [redacted] $\log_{10}$ IU/L reduction). Similarly, participants in the bulevirtide 2 mg arm experienced a larger mean decrease from baseline in ALT levels by Week 48 than participants in the delayed treatment arm (bulevirtide 2 mg: [redacted] U/L; delayed treatment: [redacted] U/L).

Table 13. Change from baseline in HDV RNA and ALT levels, MYR 301 full analysis set

Median (IQR) change from baseline	Delayed treatment (n=51[a])	Bulevirtide 2 mg (n=49[b])
HDV RNA, $\log_{10}$(IU/L)		
Week 4	[redacted]	[redacted]
Week 8	[redacted]	[redacted]
Week 16	[redacted]	[redacted]
Week 24	[redacted]	[redacted]
Week 32	[redacted]	[redacted]
Week 40	[redacted]	[redacted]
Week 48	[redacted]	[redacted]
ALT, U/L		
Week 4	[redacted]	[redacted]
Week 8	[redacted]	[redacted]
Week 16	[redacted]	[redacted]
Week 24	[redacted]	[redacted]
Week 32	[redacted]	[redacted]
Week 40	[redacted]	[redacted]
Week 48	[redacted]	[redacted]

[a] Because of missing data, n<51 for many timepoints. The minimum n was 47 across all timepoints.

[b] One participant had a missing ALT measurement, so the maximum number of participants informing the estimates for change from baseline in ALT levels was 48. Because of other missing data, the minimum n was 44 across all timepoints.

Source: CSR Tables 14.2.3.3-19 and 14.2.3.4-9

Abbreviations: ALT: alanine aminotransferase; CI: confidence interval; HDV: hepatitis delta virus; LS: least squares

In response to clarification questions posed by the EAG, the company provided additional data on the temporal pattern of participants' response rate. The EAG comments on two features of participants' responses: the longer time taken for participants to achieve virologic rather than biochemical response, and the loss of response for some participants.

First, the responder analysis suggests that ALT normalisation precedes virologic response for many participants, which was contradictory to the expectations of the EAG's clinical experts, and the company's own submission ("ALT normalisation can be viewed as a lagging indicator of treatment response"). This was particularly pronounced at Week 16, at which point [redacted] in the bulevirtide 2 mg arm achieved ALT normalisation, but only [redacted] had achieved a virologic response. However, the EAG notes that for many participants it may have been easier to achieve a biochemical response than a virologic response, because the virologic response required a $2\log_{10}$ (99%) reduction from baseline in HDV RNA levels, whereas the biochemical response only required a participant's ALT level to fall below the ULN. The EAG notes that the change from baseline in mean HDV RNA levels of participants in the bulevirtide 2 mg arm suggests there was a fast acting, but sub-threshold decrease for most participants [redacted] (Table 6).

Second, having achieved a complete ([redacted]), virologic ([redacted]) or biochemical response ([redacted]) at Week 24, [redacted] subsequently lost their complete response, [redacted] lost their virologic response and [redacted] lost their biochemical response ([redacted]) by Week 48 (Figure 1). These data question the extent to which patients treated with bulevirtide 2 mg will experience a sustained response over the treatment period.

Figure 2. Evolution of response amongst patients from Week 24 to Week 48 in the bulevirtide 2 mg treatment group (MYR 301). Reproduced from the Company's response to clarification questions (Figure 7)

Abbreviations: ALT: alanine aminotransferase; CR: combined response; NR: non-response; VR: virologic response; W24: Week 24; W48: Week 48.

3.3.2 Response rates by METAVIR stage and cirrhosis subgroups

In contrast to the decision problem and the company's economic model, at least [redacted] participants in MYR 301 had baseline METAVIR stages F0 and F1 (Section 3.2.1.2, Table 4), in the bulevirtide 2 mg and delayed treatment arms. [redacted] of these participants were in the bulevirtide 2 mg arm and [redacted] were in the delayed treatment arm. The EAG notes two concerns about the presence of these participants in MYR 301:

- Patients with lower METAVIR fibrosis scores (F0 and F1) may be more likely to achieve biochemical response because they are likely to be closer to the threshold at baseline. This would cause the trial to overestimate the efficacy of bulevirtide 2 mg in patients with F2 fibrosis score and above, i.e., in the population under consideration;
- Participants with stage F0 and F1 were more common in the non-cirrhotic subgroup of the bulevirtide 2 mg arm ([redacted]) compared to the

delayed treatment arm ([redacted], Table 4), which may have caused a bias in favour of bulevirtide 2 mg over delayed treatment in the non-cirrhotic subgroup.

The EAG requested that the company provide response rate data and baseline ALT levels for MYR 301 participants by METAVIR fibrosis stage at the clarification stage, but the company declined to provide these data. Instead, the company highlighted how METAVIR staging data were only available for [redacted] of 150 subjects ([redacted]) in the MYR 301 study population, making robust comparisons between categories challenging, something they indicated was further exacerbated by heterogeneity of the patient characteristics across METAVIR groups.

The EAG agrees with the company that making robust conclusions from these data would be challenging, however, having these data would be the only direct method of assessing whether the majority of the treatment effect from MYR 301 could be attributable to a subset of participants that are not within the population of interest. The EAG also notes that while METAVIR data were missing at baseline for[redacted]) participants, [redacted] of these participants with missing data had cirrhosis at baseline, which is considered as equivalent to METAVIR stage F4 (CS Table 1 and Section B.2.7). In contrast, the amount of missing data in the non-cirrhotic subgroup was [redacted].

In lieu of the response data by METAVIR fibrosis stage, the EAG considers the subgroup analyses by cirrhosis to be the best proxy for estimating the contribution of participants with METAVIR stages F0 and F1 to the overall trial results. F0 and F1 participants comprised at least [redacted] of participants in the non-cirrhotic subgroup (with [redacted] datapoints missing), compared to at least [redacted] of participants in the cirrhotic subgroup (with [redacted] datapoints missing, and most missing data expected to be stage F4).

The combined response rate at Week 48 was higher in the non-cirrhotic subgroup ([redacted]) than the cirrhotic subgroup ([redacted]) for the bulevirtide 2 mg arm (Table 7). This raises the possibility that a proportion of the complete response in MYR 301 is attributable to non-cirrhotic F0 and F1 participants who are outside of the company's proposed population. On average, non-cirrhotic participants were younger (mean age [SD]: [redacted]) and had lower ALT levels (mean [SD]: [redacted]) than cirrhotic patients (mean age [SD]: [redacted]; mean ALT [SD]:[redacted]) in the bulevirtide 2 mg arm. The EAG notes that the reason for the larger complete response in the

non-cirrhotic subgroup was due to the non-cirrhotic subgroup having more biochemical responders ([redacted]) than the cirrhotic subgroup ([redacted]), rather than more virologic responders. All Week 48 response data, by cirrhosis subgroup, are presented in Table 7.

Table 14. Virologic, biochemical and combined response in MYR 301 at Week 48 by baseline cirrhosis status

Arm	Responders at Week 48, n (%)	
	Participants with cirrhosis	Participants without cirrhosis
HDV RNA decrease by ≥2log$_{10}$ IU/mL or undetectable HDV RNA		
Delayed treatment	[redacted]	[redacted]
Bulevirtide 2 mg	[redacted]	[redacted]
ALT levels within the upper level of normal		
Delayed treatment	[redacted]	[redacted]
Bulevirtide 2 mg	[redacted]	[redacted]
Combined response		
Delayed treatment	[redacted]	[redacted]
Bulevirtide 2 mg	[redacted]	[redacted]

Source: CSR 9.5.1, 9.5.2.2, 9.5.3.1, Tables 14.2.1-7, 14.2.1-9, 14.2.2.2-5 and 14.2.2.2-7
Abbreviations: ALT: alanine aminotransferase; HDV: hepatitis delta virus

In summary, the EAG notes that:

- At least [redacted] of participants in MYR 301 had baseline METAVIR fibrosis of F0 or F1, i.e., were outside of the population focused on by the company;
- Response data were not made available by METAVIR fibrosis stage, making it uncertain how generalisable the results of MYR 301 are to the company's proposed population;
- Complete response rates were greater in the subgroup that included a large proportion of F0 and F1 participants (the non-cirrhotic subgroup), and hence the overall estimate of complete response from MYR 301 may overestimate the clinical efficacy of bulevirtide for patients with METAVIR staging F2 and above;
- Nevertheless, there was a substantial treatment benefit of bulevirtide 2 mg in the cirrhotic subgroup over delayed treatment, and a substantial benefit in virologic response.

3.3.3 Liver stiffness and change from baseline in METAVIR staging

The company reported the change from baseline in liver stiffness at Week 48 as a secondary endpoint, and the change from baseline in METAVIR staging as an exploratory endpoint. Compared to the delayed treatment arm (mean [SD]: [redacted] kPa), the bulevirtide 2 mg arm experienced [redacted] in liver stiffness from baseline ([redacted] kPa). METAVIR fibrosis staging data at both baseline and Week 48 were available for [redacted] of patients across the bulevirtide 2 mg and delayed treatment arms of MYR 301. At Week 48, [redacted] of participants had an improved METAVIR fibrosis stage compared to baseline in the bulevirtide 2 mg arm, [redacted] of participants experienced no change and [redacted] of participants experienced a worsening of METAVIR fibrosis stage. In the delayed treatment arm, METAVIR fibrosis stages had improved for [redacted] of participants at Week 48 compared to baseline, had not changed for [redacted] of participants and had worsened for [redacted] of participants.

The EAG asked the company to clarify why a large proportion of participants with METAVIR staging data in the delayed treatment arm showed an improvement in fibrosis score at Week 48 compared to baseline. The company suggested that this may be a result of ongoing nucleos(t)ide analogue therapy to treat the underlying chronic hepatitis B infection (response to clarification question A9). The EAG notes that the same rationale could explain some of the improvement in METAVIR fibrosis staging for participants in the bulevirtide 2 mg arm. The EAG's clinical experts note that this this may be related to the insensitivity of the FibroScan.

3.3.4 Health related quality of life

Health related quality of life (HRQoL) was assessed using the EuroQoL 5-Dimension 3-Level (EQ-5D-3L) and the EQ Visual Analogue Score (VAS). There were [redacted] in any of the five EQ-5D-3L dimensions at Week 48, although the company noted that participants in the bulevirtide 2 mg arm experienced a [redacted], where [redacted] participants reported some problems, to Week 48, where [redacted] participants reported some problems, than in the delayed treatment arm (Baseline: [redacted] participants reported some problems; Week 48: [redacted] participants reported some problems). Similarly, there was [redacted] in change from baseline VAS scores at Week 48 in the bulevirtide 2 mg arm ([redacted]) and the delayed treatment arm ([redacted]). The company states that these HRQoL measures may lack the ability to detect meaningful differences in HRQoL between

the cirrhotic and non-cirrhotic subgroups in MYR 301, and HRQoL data from MYR 301 were, therefore, not used in the economic model (Section 4.2.8). The EAG does not consider the HRQoL data from MYR 301 to lack face validity. The EAG's clinical experts stated that the impact on QoL of different levels of fibrosis is likely very small, it is the underlying HDV infection that is more likely to result in reduced QoL, not the presence or absence of differing degrees of fibrosis.

3.3.5 Safety data

Compliance with bulevirtide was high across the 48 weeks in the bulevirtide 2 mg arm (mean compliance [SD]: [redacted]), and the mean number of missed bulevirtide doses was [redacted], with a maximum of [redacted]. This is a high rate of compliance to bulevirtide given that bulevirtide was administered to participants daily over 48 weeks, and there were no reports of participants having dose reductions or interruptions while on bulevirtide 2 mg. One participant from the bulevirtide 2 mg arm prematurely withdrew from the study by Week 48, as they withdrew consent, however no participant discontinued because of adverse events (AEs).

AEs that occurred in MYR 301 were reported in section 3.2.2.10 of the CS (safety analysis set), and they are reproduced in Appendix Table 8 (overview of AEs) and Table 9 (individual AEs).

Overall, the total number of AEs was [redacted] in the delayed treatment arm [redacted] than the bulevirtide 2 mg arm [redacted] although, the percentage of participants who had any AE was [redacted] Injection site reactions were reported for [redacted] of 49 participants in the bulevirtide 2 mg arm. The majority of AEs were Grade 1 (mild) or Grade 2 (moderate) for all participants, with only [redacted] None of these serious AEs were treatment related, as determined by the investigators.

Bile salt elevations above the ULN, an AE that is expected to occur because bulevirtide inhibits the bile acid transporter (the sodium taurocholate cotransporting polypeptide), were not reported as AEs for MYR 301 if they were asymptomatic and judged by the investigator to be clinically insignificant, but the change from baseline in total blood bile salts for the MYR 301 arms were reported in Table 14.3.3.3-1 of the CSR:

[redacted] Skin and subcutaneous disorders, which are associated with

bile salt elevations, were observed in [redacted] in the bulevirtide 2 mg arm, but [redacted] in the delayed treatment arm, at Week 48.

Other notable AEs included measures of hepatic safety and eosinophilia. In-line with the EAG's comment on the inconsistency of participants ALT normalisation (Section 3.2.2.1), increased ALT meeting the definition of an AE was reported [redacted] participants at Week 48. This contributed to a total of [redacted] participants ([redacted]) experiencing a potential hepatic flare in the delayed treatment arm, compared with [redacted] participants ([redacted]) in the bulevirtide 2 mg arm. Eosinophilia was reported in [redacted] participants in the bulevirtide 2 mg arm, but in no participants in the delayed treatment arm.

The company only included severe (Grade 3 or above) AEs in their model, which is discussed in Section 4.2.7. Overall, the EAG agrees with the company that, although some AEs were more common in bulevirtide 2 mg treated participants than delayed treatment patients, these events were not considered severe by the trial investigators, and thus bulevirtide had an acceptable safety profile over the 48 weeks. The EAG notes, however, that long-term data on the safety of bulevirtide 2 mg are not yet available.

3.3.6 Resistance data

The company stated that developing resistance to bulevirtide would be unlikely, as the mechanism of action of bulevirtide would require a mutation within the HBV envelope protein for resistance to emerge (response to consultee and commentator comments on the draft scope). The EAG's clinical experts concurred that it is not expected that patients would develop resistance to bulevirtide. Nevertheless, the clinical data from MYR 301 highlighted that, even in the absence of developed resistance, participants were able to lose their virologic response. Figure 1 shows that [redacted] participants ([redacted]) who had either a combined or virologic response at Week 24 lost at least their virologic response by Week 48. Similarly, in response to a clarification question, the company reported that nine patients in the bulevirtide 2 mg arm experienced virologic breakthrough across the first 48 weeks of MYR 301. These data show that even if resistance mutations against bulevirtide are unlikely, this does not guarantee a sustained virologic response.

3.4 Conclusions of the clinical effectiveness section

The evidence submitted by the company in support of the clinical efficacy and safety of bulevirtide in the treatment of chronic hepatitis D (CHD) is primarily derived from the open label randomised

controlled trial (RCT) MYR 301. The EAG considers MYR 301 to be a good quality trial that provides evidence for the clinical benefits of bulevirtide 2 mg over best supportive care. The MYR 301 trial shows that bulevirtide treatment leads to statistically significantly more patients with a complete response, that is both a virological (decrease or undetectable HDV levels) and a biochemical (ALT normalisation) response compared with BSC at 24 weeks and 48 weeks of treatment.

Virological and biochemical response can be considered surrogate outcomes of the prevention of complications of liver disease, such as HCC and death, which are not feasible to assess directly in clinical trials given liver disease complications can take years to develop. There is evidence linking virological and biochemical response with liver disease progression outcomes in people with HBV or HCV, and the EAG's clinical experts agree it would be reasonable to assume the same relationship is true for these outcomes for HDV. However, the EAG notes that the nature of the correlation between the surrogate outcomes and the long-term outcomes of liver disease complications remains uncertain.

Although MYR 301 is an open label trial, the risk of bias due to the lack of blinding is low for the key efficacy outcomes of virological and biochemical response but likely to be higher for patient reported HRQoL and adverse events. However, it is not possible to rule out that participants' behaviour and lifestyle choices may have differed between those who were treated with bulevirtide and those who were not, which could affect ALT levels.

Different thresholds were used to define the ULN for ALT response in the trial depending on region and sex. The EAG's clinical experts confirm that there is large variability between labs and between countries in ALT assessments and that there is a lack of consensus around what thresholds should be used to define ALT normalisation. The EAG notes that while this is unlikely to bias results in favour of bulevirtide, it may make the interpretation of the results more difficult to apply to UK clinical practice.

Patients enrolled in MYR 301 were adults with CHD and compensated liver disease, in line with the population specified in the NICE final scope. However, the company has focused on a population narrower than the scope and narrower than the population in the trial, restricting it to adults with CHD with evidence of significant fibrosis (METAVIR fibrosis stage of at least F2) and who have experienced treatment failure with IFN-based treatment or who were contraindicated to or intolerant of IFN-based treatment. Overall, the EAG considers this narrower population to be

reasonable given this represents a subset of patients covered in the conditional marketing authorisation with a particularly high unmet need in terms of treatment options. The treatments currently available for these patients are limited to treatment of their concomitant HBV infection. However, data limited to the narrower population focused on by the company are not available from the trial. Data on METAVIR fibrosis stage was only available for [redacted] of participants and, although subgroup data are available for participants previously treated with IFN therapy, this did not capture participants who were intolerant or for whom IFN therapy was contraindicated.

It is unclear if and to what extent the effectiveness of bulevirtide differs between the full trial population and the narrower population the company is focusing on. *Post-hoc* subgroup analyses amongst IFN-based therapy naïve patients and those with prior IFN-based therapy exposure suggests a numerical difference with a larger proportion of patients achieving a combined (virological and biochemical) response with bulevirtide treatment among those with prior IFN-based therapy exposure. For participants with METAVIR fibrosis staging data available at baseline there was a relatively large imbalance between the treatment arms: [redacted] baseline METAVIR fibrosis stage of F0 or F1 in the bulevirtide 2 mg arm and the delayed treatment arm, respectively. It may be easier for patients in lower METAVIR fibrosis stages (F0 and F1) to achieve biochemical response as they are likely to be closer to the ALT normalisation threshold. This would cause a potential overestimate of the efficacy of bulevirtide 2 mg compared with BSC in the full trial population compared with patients with METAVIR fibrosis stage of F2 or above, i.e., the population the company is focusing on. The imbalance in the proportion of patients with F0 and F1 was even more pronounced in the non-cirrhotic subgroup, defined by the company as METAVIR fibrosis stage of F0 to F3. Whereas the cirrhotic subgroup, defined as METAVIR fibrosis stage F4, should be unaffected by the imbalance. The prespecified and stratified subgroup analyses of cirrhotic and non-cirrhotic patients show a numerical difference with a larger proportion of patients achieving a combined response with bulevirtide treatment among those without cirrhosis compared to those with cirrhosis at baseline. The EAG, therefore, recommends that the company includes a scenario analysis in the model focused on the cirrhotic subgroup. Although, the EAG acknowledge the limitations of this analysis in that it excludes participants with METAVIR stage F2 an F3.

Temporal data of response from MYR 301 show that some patients lost either biochemical or virological response between week 24 and week 48 while on bulevirtide treatment, that is, complete response was not sustained for everyone while on treatment. This is important as the company has assumed in the model that patients who achieve a complete response will only lose it if they

discontinue treatment, based on a 1.03% discontinuation rate in the trial ([redacted], no participant discontinued because of adverse events). However, the EAG base case uses the observed trial data to inform the transitions between non-responders, partial responders and complete responders.

The EAG also highlights the uncertainty around the optimal duration of bulevirtide treatment. The company reports that treatment should be continued as long as associated with a clinical benefit and the SmPC states that discontinuation of treatment should be considered in case of loss of virological and biochemical response. In the MYR 301 trial participants are scheduled to continued bulevirtide treatment up to 144 weeks. The EAG assumes that treatment is continued for the full trial duration irrespective of response, i.e. also for non-responders, partial responders and complete responders who lose either their virological and/or biochemical response while on treatment. However, in the economic model the company assumes that patients who haven't responded by week 48 will discontinue treatment at that time point, patients with a partial response are assumed to discontinue treatment at 72 weeks and complete responders are assumed to continue treatment indefinitely. The EAG's clinical experts state that in clinical practice, response is likely to be assessed after 12 weeks and 24 weeks of treatment, but that it is reasonable to make a final judgement around treatment discontinuations for non-responders at 48 weeks. It is less clear for how long to continue treatment for patients who achieve a virological response but not a biochemical response, but it may be reasonable to assess whether to continue treatment of partial responders at 72 weeks. Later data cut offs for MYR 301 may provide more robust data on patients who lose response while on treatment and data to inform the best timepoint for partial responders to stop treatment.

4 Cost effectiveness

Table 15 presents the incremental cost-effectiveness results of the company's updated (post clarification) base case results. A proposed confidential patient access scheme (PAS) discount of [redacted] for bulevirtide is applied in the company's base case and is therefore reflected in the results presented in this report. The company also presents the net health benefit (NHB) of bulevirtide and this can be found in Table 71 of the company submission (CS).

Table 15. Company's base case results (updated post clarification)

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Deterministic results							
BSC	[redacted]	8.14	[redacted]	-	-	-	-
Bulevirtide	[redacted]	12.96	[redacted]	[redacted]	4.82	[redacted]	£40,562
Probabilistic results							
BSC	[redacted]	N/a	[redacted]	-	-	-	-
Bulevirtide	[redacted]	N/a	[redacted]	[redacted]	N/a	[redacted]	£42,239

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life years; N/a, not applicable QALY, quality adjusted life year

4.1 EAG comment on the company's review of cost effectiveness evidence

The company performed a single systematic literature review (SLR) to identify evidence on efficacy, safety, and tolerability of pharmacological treatments for adults with chronic hepatitis delta (CHD) and used this search to identify relevant cost-effectiveness and health-related quality of life (HRQoL) studies. The primary search was initially conducted in October 2020 and was last updated in December 2021.

A summary of the ERG's critique of the methods implemented by the company to identify relevant evidence is presented in Table 16. Due to time constraints, the ERG was unable to replicate the company's searches and appraisal of identified abstracts.

Table 16. ERG's critique of company's systematic literature review

Systematic review step	Section of CS in which methods are reported			EAG assessment of robustness of methods
	Cost effectiveness evidence	HRQoL evidence	Resource use and costs evidence	
Search strategy	Appendix D	Appendix D	Appendix D	The company performed one search for clinical and cost-effectiveness data that

				was not restricted by study design filters or outcomes. This approach means that a broad range of evidence would be identified, but the use of economic search filters may have made the SLR more efficient.
Inclusion/exclusion criteria	Appendix G and Table 38 of the company clarification response	Appendix H and Table 39 of the company clarification response	Appendix G and Table 38 of the company clarification response	Appropriate
Screening	Appendix G	Appendix H	Appendix G	Appropriate
Data extraction	Table 33 of the CS	Appendix H	Appendix I	Appropriate
Quality assessment of included studies	Appendix G	Appendix G	Appendix G	Appropriate

Abbreviations: CS, company submission; EAG, evidence review group; HRQoL, health related quality of life.

The company's primary search identified 13 cost-effectiveness studies, seven HRQoL studies and eight costs studies. However, none of the included studies were used to inform the cost-effectiveness analysis. The company stated that of the identified cost-effectiveness studies, none were suitable to address the decision problem.

For HRQoL studies, the company found none of the seven included studies provided suitable CHD-specific health state utility data, including their own MYR 301 and MYR 204 studies. However, the EAG considers that the dismissal of the MYR 301 and MYR 204 studies was because extracted utility data were for baseline and Week 24 rather than for Week 48 and stratified by cirrhosis status. Nonetheless, the company did perform additional HRQoL analyses on the MYR 301 data for use in the model and this is described further in Section 4.2.7. Additionally, the company performed a meta-analysis of HBV and HCV utility values for use in the model, also described in Section 4.2.7.

Lastly, none of the eight cost studies identified by the company's SLR provided UK-specific cost data relevant to CHD patients. Instead, the company sought advice from clinical experts and performed targeted literature search for health-state costs and this is described further in Section 4.2.8.

4.2 Summary and critique of company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 17 summarises the EAG's appraisal of the company's economic evaluation against the requirements set out in the NICE reference case checklist for the base-case analysis, with reference to the NICE final scope outlined in Section 2.

Table 17. NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	All relevant health effects for adult patients with CHD have been included.
Perspective on costs	NHS and PSS	All relevant costs have been included and are based on the NHS and PSS perspective.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Cost-utility analysis has been provided by the company. Fully incremental analysis not required as there is only one relevant comparator in the analysis.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Age at baseline in the model was 35.1 years and the model time horizon was 65 years.
Synthesis of evidence on health effects	Based on systematic review	The company performed an appropriate systematic review.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	QALYs based on a meta-analysis of CHB utility values. The EAG's preference is to use the trial EQ-5D data directly.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	QALYs based on a meta-analysis of CHB utility values. The EAG's preference is to use the trial EQ-5D data directly.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	QALYs based on a meta-analysis of CHB utility values. The EAG's preference is to use the trial EQ-5D data directly.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	The economic evaluation matches the reference case.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be	Costs included in the analysis have been sourced using NHS reference costs[33] BNF[34] and

	valued using the prices relevant to the NHS and PSS	published literature and are reported in pounds sterling for the price year 2020.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Discount rate of 3.5% has been used for both costs and health effects.

Abbreviations: EAG, evidence review group; NHS, national health service; PSS, personal social services; QALY, quality adjusted life year

4.2.2 Population

The population considered in the NICE final scope consists of adults with CHD who have compensated liver disease, which reflects the company's conditional marketing authorisation. However, the population considered in the model is restricted to adults with CHD who have compensated liver disease and evidence of significant fibrosis (METAVIR stage greater than or equal to F2), whose disease has responded inadequately to IFN-based therapy, or who are ineligible to receive IFN-based therapy due to intolerance or contraindication. Therefore, the company restricted the scope population to patients who are intolerant/contraindicated or have failed previous IFN-based therapy.

The EAG's clinical experts advised that IFN-based treatment is not well tolerated and there will be several reasons why patients may be ineligible for treatment. The EAG's clinical experts also advised that bulevirtide will likely be used in patients who cannot have or have not responded adequately to IFN-based treatment as no other treatment options are available, therefore, the EAG is satisfied with the company's restriction of the scope to the pre-treated or intolerant to IFN-based therapy population.

The company originally used clinical effectiveness data from the subgroup of patients in MYR 301 who were pre-treated with IFN to estimate the cost effectiveness of bulevirtide. As discussed in Section 2.3.1, the EAG considers the full trial population to be more relevant and more robust than the subgroup of patients who previously had IFN-based therapy in the trial. Therefore, during clarification, the EAG requested that the company used the clinical effectiveness data on response; partial response; and no response from the full trial population to estimate the transition probabilities in both arms of the model. The company agreed with the EAG and updated their economic analysis to be based on the MYR 301 full trial population.

In MYR 301, baseline fibrosis stage was missing for 49% of patients across the delayed treatment and bulevirtide 2 mg arms of the trial. However, as discussed in Section 3, the trial included people with any degree of fibrosis – of those in MYR 301 where METAVIR staging was performed at baseline, a substantial proportion in each treatment arm were F0 or F1 stage, with the proportion being higher in the bulevirtide arm. The EAG is therefore concerned that the (modelled) population in MYR 301 is not representative of the population being proposed for the company's indication of bulevirtide. The trial population has less severe liver disease than the indicated population and thus is expected to have better prognosis, and potentially experience a higher response rate with bulevirtide given that these patients are likely to be closer to the ALT normalisation threshold for response (see Section 3.2.2 for more details).

Given that participants with stage F0 and F1 were more common in the non-cirrhotic subgroup of the bulevirtide 2 mg arm ([redacted]) compared to the delayed treatment arm ([redacted], Table 4 in Section 3.3), this might have caused a bias in favour of bulevirtide 2 mg over delayed treatment in the non-cirrhotic subgroup.

As explained in Section 3, the EAG is concerned that complete response rates were greater in the non-cirrhotic subgroup, hence the overall estimate of complete response from MYR 301 may overestimate the clinical efficacy of bulevirtide for patients with METAVIR staging F2 and above. Therefore, the EAG requested that the company undertook a subgroup analysis by cirrhosis presence at baseline to be the best proxy for estimating the contribution of participants with METAVIR stages F0 and F1 to the overall trial results. The company did not undertake the analysis and therefore the EAG asks that the company reconsiders this at technical engagement.

To inform the baseline distribution of patients amongst fibrosis stages F2 to F4 in the economic model, the company decided to use data from published literature, as MYR 301 did not include patients from the UK. The company used a study by Spaan *et al*. 2020 to inform the baseline cirrhosis estimate in the model and adjusted the non-cirrhotic patients to be distributed according to Romeo *et al*. 2009, which provided a distribution of HDV patients by fibrosis stage (F0 to F4). The resulting baseline distribution used by the company was 60% of F4 patients; 24% of F3 and 17% of F2 patients. As noted in Section 4.2.5, the EAG is concerned with the lack of justification for what seems an unsystematic approach to choosing sources for model input parameters.[35,2]

The EAG encountered a small error in the use of the Spaan *et al*. 2020 estimate as in the study 23 out of 46 patients (50%) in the actively replicating HDV detectable HDV RNA and/or anti-HDV-IgM subgroup were cirrhotic at baseline, however, this was incorrectly assumed to be 46% in the company's calculations. The impact of the EAG correction is reported in section 6.1.

The company also used Spaan *et al*. to inform baseline age in the model (35.1 years) and the proportion of males (58.7%). While the EAG's clinical experts considered that the baseline characteristics included in the company's model were representative of the UK population, they noted that the baseline characteristics in the trial were not clinically implausible. The proportion of males in MYR 301 was similar to that assumed in the model, however, the mean age in the MYR 301 population was 42 years and 47% of patients had cirrhosis at baseline (based on clinical assessment).

Given the considerable impact that baseline age and cirrhosis distribution have on the economic results (See Section 6.3 and Section 7.1.1), the EAG recommends that the committee's clinical experts assess the plausibility of the population characteristics in both scenarios.

4.2.3 Interventions and comparators

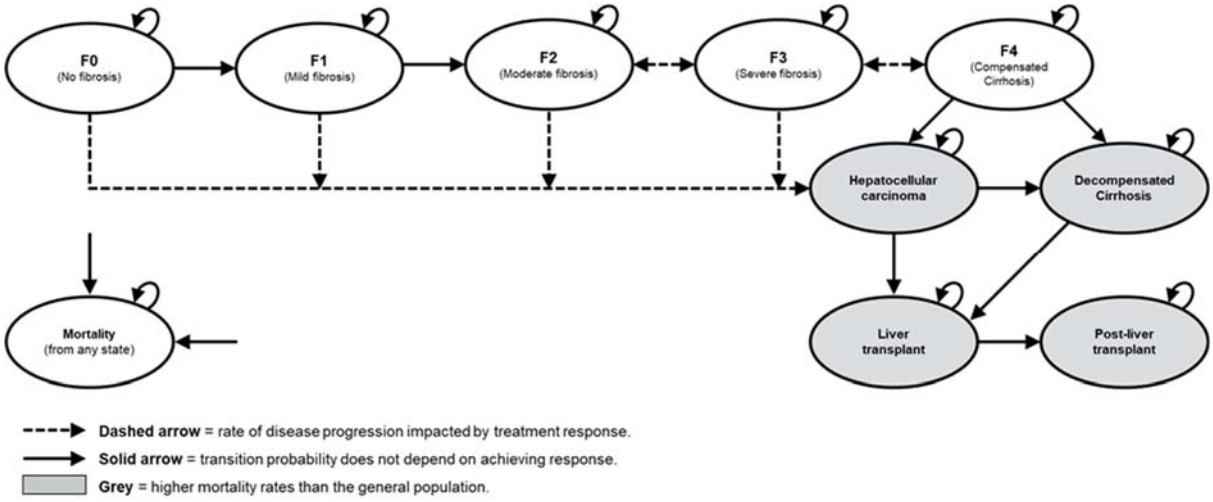
The intervention considered for the economic analysis is bulevirtide 2 mg once daily. Bulevirtide is delivered by subcutaneous (SC) injection as monotherapy or with concomitant nucelos(t)ide analogue (NA) for treatment of underlying HBV infection. As per the summary of product characteristics (SmPC), bulevirtide should be continued as long as associated with clinical benefit.

The comparators listed in the NICE final scope are best supportive care (BSC) and peginterferon alfa-2a (PEG-IFN). However, the company has based their analysis of bulevirtide against a comparison of BSC only given that the population of interest is restricted to CHD patients whose disease has responded inadequately to IFN-based therapy, or who are ineligible to receive IFN-based therapy. As such, the EAG considers that BSC is an appropriate comparator for the cost-effectiveness analysis.

4.2.4 *Modelling approach and model structure*

A single *de novo* Markov model was developed in Microsoft© Excel to assess the cost-effectiveness of bulevirtide compared with BSC. Figure 3 presents the model schematic.

Figure 3. Model schematic (reproduced from Figure 15 of the company clarification response)



Note: The EAG notes that the solid arrow from the hepatocellular carcinoma health state to the decompensated cirrhosis health state is an error, and should instead be in the opposite direction, i.e., patients can transition from the decompensated cirrhosis to the health hepatocellular carcinoma health state, and not the other way around.

The chosen cycle length in the company's model was 24 weeks as the model was based on a cohort Markov model, with two points for assessing response and treatment discontinuation. At 48 weeks in the model patients have an initial assessment for treatment response, based on data from the MYR 301 trial. Patients who have a complete response [(CR) defined as HDV-RNA undetectability or ≥2-log10 IU/ml decline and ALT normalisation] or a partial response [(PR) defined as HDV-RNA undetectability or ≥2-log10 IU/ml decline] remain on treatment until the next assessment point at 72 weeks. Non-responders (NR) are identified at week 48 and are assumed to discontinue treatment permanently (if on bulevirtide) and begin BSC. From week 48 onwards, NRs are assumed to remain in that category and cannot gain response. At week 72, patients have their final assessment of response in the model, when they are categorised as either NRs or CRs, based on data extrapolated from MYR 301. Patients categorised as CRs continue treatment (unless they discontinue for reasons other than disease progression as discussed in Section 4.2.10), whereas NR start receiving BSC.

Patients enter the model in one of three fibrosis METAVIR stages (F2, F3 and F4). For patients with a CR, disease progression is assumed to stop, which means that patients cannot progress through the different METAVIR stages, as per the dotted arrows in Figure 3. Additionally, CR can also regress

through the fibrosis health states (i.e., F4 to F3 and F3 to F2), and have a 0% probability of developing hepatocellular carcinoma (HCC) from any METAVIR stage. Patients with a PR or NR can progress through the fibrosis health states and have an additional per cycle risk of developing HCC from any fibrosis state. From any fibrosis health state, the company has also assumed an annual probability of spontaneous clearance (HbsAg seroclearance). Please refer to Section 4.2.5 of the EAG report for further details on how health state transition probabilities were implemented in the model.

Once in the HCC state, patients can remain in the state until death or transition to the liver transplant (LT) health state. In the LT health state, patients experience a risk of death related to transplant or complications following transplant (such as graft rejection). If patients in the LT health state survive for one year, they transition to the post-liver transplant (PLT) health state. Patients remain in the PLT health state until death.

Risk of liver-related death is applied to the F4, decompensated cirrhosis (DC), HCC, LT and PLT health states. Additionally, for all patients in the model, background mortality is applied (see Section 4.2.6 for further details).

The model time horizon was set to 65 years (mean age in the model at baseline was assumed to be 35 years as per Section 4.2.2). The perspective of the analysis was based on the UK NHS, with costs and benefits discounted using a rate of 3.5%, as per the NICE reference case.

4.2.4.1 EAG critique

During clarification, the EAG requested a justification for the company's choice of timeframe for extrapolating treatment effectiveness in the model. The company reported to have observed a plateau in extrapolated rates of CR soon after 96 weeks (3% increase between week 72 and 96), thus thought it was appropriate to limit treatment response to 72 weeks in the model. Furthermore, the company noted that patients from the MYR 301 study continue to be followed up and data for 96 weeks of treatment are anticipated to become available in [redacted]. The EAG discusses in detail the company's approach to estimating and extrapolating treatment effectiveness in the model in Section4.2.5 of the EAG report, however, notes that due to uncertainty in the extrapolations of treatment effectiveness beyond 48 weeks, a more robust method of analysis would have been to limit the timeframe for assessing response to 48 weeks in the model. This would have been consistent with the available trial data (for 48 weeks) and with clinical expert opinion provided to

the EAG that response (or lack thereof) to treatment is assessed well before 48 weeks, at 3 or 6 months. Therefore, the EAG has conducted a scenario analysis where 48 weeks is the maximum timeframe for assessing final response to treatment (results of the analysis are reported in Section 6.2).

Even though the company model included the F0 and F1 states, patients never occupy these states in the analysis as 0% of patients are assumed to enter the model in these fibrosis states and CRs in the F2 category are assumed to not be able to regress to any lower states. Therefore, the F0 and F1 states are effectively not included in the company's analysis.

The EAG notes that the economic model in TA173 (tenofovir disoproxil for the treatment of chronic hepatitis B) allowed patients to transition from the HCC to the LT state, whereas TA153 (entecavir for the treatment of chronic hepatitis B) only modelled patients' transitions from the DC to the LT state, and did not consider that HCC patients were eligible to receive a LT. The EAG's clinical experts stated that the indications for LT are decompensation; or HCC fitting specific criteria. Therefore, the EAG finds the company's approach reasonable.

Finally, the EAG notes that in previous TAs, as in the present company's model, patients could only remain in the HCC state or transition to the LT state. NRs in the model have a probability of LT of 0.72% per 24-week cycle and a probability of 68% of remaining in the HCC state, with a 32% probability of death every cycle. The EAG is unclear on the clinical plausibility of this assumption, as the Barcelona Clinic Liver Cancer staging and treatment recommendations for HCC (as reported in TA551) suggest that patients, especially in the earlier stages of HCC, can be cured through other procedures such as resection or ablations. Furthermore, patients in the more advanced stages of the cancer can transition to a progression-free state of the disease when treated. The EAG notes that the company assumption, if not clinically plausible, is biased towards bulevirtide as a higher proportion of patients in the BSC arm of the model experience HCC and remain in that same state, experiencing very high costs and a low utility value. Therefore, the EAG recommends that the company validates this assumption at technical engagement and includes a scenario analysis in the model where a proportion of HCC patients can transition to a cure or a progression-free state of the disease.

4.2.5 Treatment effectiveness

The company used multiple sources of evidence to estimate treatment effectiveness in the model. Overall response (regardless of fibrosis stage) was informed by data from the full population in MYR 301, while transitions between the different fibrosis stages and more severe disease complications were informed by external data sources.

4.2.5.1 Estimation of response during the initial 72 weeks of the model

The company used trial data to estimate response to treatment at 24 and 48 weeks in the model. However, the company assumed that patients could not lose response during this period, therefore, the trial data was not directly used to estimate transition probabilities (TPs) in the model.

Patients had their first assessment of response to determine treatment continuation in the model at 48 weeks. At 48 weeks, NRs were assumed to discontinue treatment, leaving CRs and PRs on treatment from that point onwards. After week 48, bulevirtide CRs could only lose response (and become NRs) if they discontinued treatment (for reasons other than disease progression), whereas CRs on BSC were assumed to not lose response after week 48. Furthermore, bulevirtide CRs were also assumed to not partially lose response and therefore could not become PRs. Consequently, after week 48 up to week 72 in the model, the only changes in treatment effectiveness in the bulevirtide arm were those captured in the TPs from PR to CR (i.e., when bulevirtide virologic responders gained complete response) and CR to NR due to treatment discontinuation.

The company extrapolated the observed trial data in order to estimate response to week 72 (the last point for assessment of response in the model). The company did this by using the EMAX function with continuity correction in the R statistical package. The company reported that, "*based on visual inspection of the pattern of observed response rates at weeks 4, 8, 16, 24 and 48, within each treatment group of MYR 301, the shape of the response rates was deemed appropriate to be fit with an EMAX function"*.

The company fitted a separate set of EMAX functions by treatment arm, estimated for both endpoints of combined and virologic response. Once the parameters of the response curve for each endpoint and treatment group were determined, the predicted response values at week 72 were derived. More details of the company's extrapolation approach can be found in Section B.3.3.2 and Appendix O of the CS.

The company provided two scenario analyses in the model, one where virologic response was selected as the definition of a complete responder; and the other where only observed data (up to week 48 in the MYR 301 trial) was used in the model.

4.2.5.2 EAG critique of estimation of response for the initial 72 weeks of the model

As discussed in detail in Section 3, the EAG notes that biochemical response in the MYR 301 trial happened earlier than virological response, with virological response showing to be more sustained than biochemical response. Notwithstanding, the EAG agrees with the company's approach of using the MYR 301 primary endpoint (i.e., the composite response endpoint) to estimate CR in the model and with the company's definition of partial response being based on virologic response. During clarification, the EAG asked the company to discuss the possibility of including biochemical response alone as PR in the model (in addition to virologic response alone). The company reported that biochemical response alone was not considered in the model as ALT levels may improve for other reasons unrelated to HDV levels, whereas a biochemical response due to HDV viral suppression requires an associated virologic response. The EAG's clinical expert agreed with the company's rationale that ALT levels can vary due to other issues such as life-style changes. The EAG notes that including biochemical response alone as PR in the model would have favoured bulevirtide.

The EAG disagrees with the company's methodology for estimating treatment effectiveness in the model. Although the EAG agrees with the use of MYR 301 data, it notes that the company's assumption of no loss of response led to the estimation of TPs which are not reflective of the data observed in the trial. The TPs used in the model (reported in Table 18 for bulevirtide) do not match the transitions observed in Figure 3 reported in the Section 3.3.1. which show that both PRs and CRs could lose response while on treatment. The EAG estimated the TPs using the trial data and presents these in Table 19. The biggest difference is in the loss of response, as the trial data showed that [redacted] of PRs and [redacted] of CRs at week 24 became NRs at week 48. Contrastingly, in the company's base case, PRs were assumed to not lose response before week 72 and only 1.03% of CRs could lose response at any cycle due to treatment discontinuation. The company also assumed that CRs could not become PRs, whereas the trial data shows that [redacted] of CRs became PRs at week 48.

Table 18. Transition probabilities in the bulevirtide arm between response categories (independent of fibrosis stage) used in the company's base case

	Transition probabilities (in %)								
Week	**NR -> PR**	**NR -> CR**	**NR -> NR^**	**PR -> PR^**	**PR -> CR**	**PR -> NR**	**CR -> PR**	**CR -> CR^**	**CR-> NR**
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
72	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
96	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*based on extrapolations

^estimated as 100% minus the sum of the other TPs within the same state

Table 19. Transition probabilities in the bulevirtide arm between response categories (independent of fibrosis stage) estimated by the EAG from trial data

	Transition probabilities (in %)								
Week	**NR -> PR**	**NR -> CR**	**NR -> NR^**	**PR -> PR^**	**PR -> CR**	**PR -> NR**	**CR -> PR**	**CR -> CR^**	**CR-> NR**
24	[redacted]	Same as company	[redacted]	Same as company	Same as company	Same as company	Same as company	Same as company	Same as company
48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

^estimated as 100% minus the sum of the other TPs within the same state

For the BSC arm the company provided the equivalent of Figure 2, as part of the clarification stage, showing the transitions observed in MYR 301 for patients in the delayed treatment arm. However, there were several discrepancies in the data between this figure and the response data presented in the CS and CSR. The EAG, therefore, used the response data provided in Table 12, however had to make assumptions about how participants moved between response states; the EAG assumed that the one patient with a CR at 48 had a VR at week 24, of the two patients with VR at week 48 one had VR also at week 24 and the other was a NR at week 24.

The values estimated by the company and the observed values from the trial estimated by the EAG for the BSC arm are consistent, with the exception of the TP between NR and PR at week 48 where the company assumed this to be 0% and the EAG estimated this to be 2.04% (Table 20 and Table 21). Nonetheless, the EAG caveats its analysis by the fact that although it is based on the trial data, assumptions had to be made around the transition of patients between response states. The EAG recommends that the company validates these transition probabilities at technical engagement. The EAG considers that the observed trial data should be used in the economic model and thus conducted a scenario analysis where the TPs reported in Table 19 and Table 21 are used in the analysis. Results are presented in Section 6.2.

Table 20. Transition probabilities in the BSC arm between response categories (independent of fibrosis stage) used in the company's base case

	Transition probabilities (in %)								
Week	**NR -> PR**	**NR -> CR**	**NR -> NR^**	**PR -> PR^**	**PR -> CR**	**PR -> NR**	**CR -> PR**	**CR -> CR^**	**CR-> NR**
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
72	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
96	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*based on extrapolations

^estimated as 100% minus the sum of the other TPs within the same state

Table 21. Transition probabilities in the BSC arm between response categories (independent of fibrosis stage) estimated by the EAG from trial data

	Transition probabilities (in %)								
Week	**NR -> PR**	**NR -> CR**	**NR -> NR^**	**PR -> PR^**	**PR -> CR**	**PR -> NR**	**CR -> PR**	**CR -> CR^**	**CR-> NR**
24	Same as company								
48	[redacted]	Same as company	[redacted]	Same as company					

^estimated as 100% minus the sum of the other TPs within the same state

Furthermore, during clarification, the EAG noted that the fitted curves with the EMAX function used by the company only provided a plausible fit to the observed data for virologic response, while the extrapolated curves for biochemical response were a poor fit (dotted orange curves in Figure 4 and Figure 5, for bulevirtide and BSC, respectively) to the observed data (dotted blue curves in in Figure 4 and Figure 5, for bulevirtide and BSC, respectively). Therefore, the EAG asked that the company reconsidered the fitted curves used in the model.

In response to the EAG's concerns, the company remained of the opinion that the EMAX function was the most appropriate to extrapolate treatment effectiveness, however, acknowledged that the fitted curves resulted in an underestimation of response at weeks 16, 24 and 40, and an overestimation of response at week 32 and 48. Therefore, the company undertook two sensitivity analysis models using the EMAX model: one excluding the observed response rate data at weeks 16, 24 and 40 (dotted green curves in in Figure 4 and Figure 5, for bulevirtide and BSC, respectively); and another analysis excluding the week 40 observed data only (dotted red curves in in Figure 4 and Figure 5, for bulevirtide and BSC, respectively). The EAG notes that Figure 4 and Figure 5 provided by the company at clarification were labelled as being the "8mg bulevirtide" curves, however, upon closer inspection the EAG considered this to be a labelling mistake as the observed data matched that provided by the company for the "2mg bulevirtide" group before clarification. Nonetheless, the EAG requests that the company confirms this.

The company concluded that, "*the first sensitivity analysis model appears to provide the best fit* [however] *given the similarity to the* [original] *model and low sensitivity of results to such a minor change, a change to the economic model was not deemed necessary*." The EAG considers the company's scenario analyses flawed, and unfit for decision making, especially with regards to the first scenario analysis where 43% of observed data points from the trial were excluded from the fitting exercise without any plausible justification. The EAG also fundamentally disagrees with the company's conclusion that the first scenario analysis (green curves) provides the best fit for the observed data and also disagrees with the assessment that the latter are similar to the original fitted curves (orange curves).

Nonetheless, the EAG acknowledges that only one data point (for each treatment arm) resulting from the company's extrapolation exercise is used in the economic model. This consists of the TP from the PR to the CR states at week 72 in the bulevirtide arm (34%) and in the BSC arm (5.32%).

Given the uncertainty in the extrapolations of the biochemical response (included in the CR endpoint) and the fact that it is only used for one cycle in the model, the EAG considers that a more robust approach would have been to only include the 48-week trial data in the model. Given that patients from the MYR 301 study continue to be followed up and that data for 96 weeks of treatment are anticipated to become available in [redacted], the EAG notes that reliable observed data to populate the model for an addition 2 cycles will become available soon.

Furthermore, as discussed in Section 4.2.10, patients in MYR 301 are scheduled to continue treatment up to 144 weeks in the trial follow-up period. Given that the SmPC for bulevirtide states that, "*The optimal treatment duration is unknown* [and that] *treatment should be continued as long as associated with clinical benefit*" there is a disconnection between the model assumption that patients could gain response up to week 72 but that PRs at that point would stop treatment as it is likely that treatment in MYR 301 carried on for a longer period of time for these patients. This reinforces the uncertainty around assumptions made for extrapolating treatment effectiveness for another cycle in the model.

Therefore, the EAG disagrees with the use of the extrapolated data in the model and considers that using 48-week data from MYR 301 is the more robust approach to estimate treatment effectiveness for bulevirtide. This assumption is reflected in the EAG's scenario using only trial data as reported in Table 19 and Table 21.

Figure 4. Observed vs predicted ALT response from EMAX models - bulevirtide (overall population)

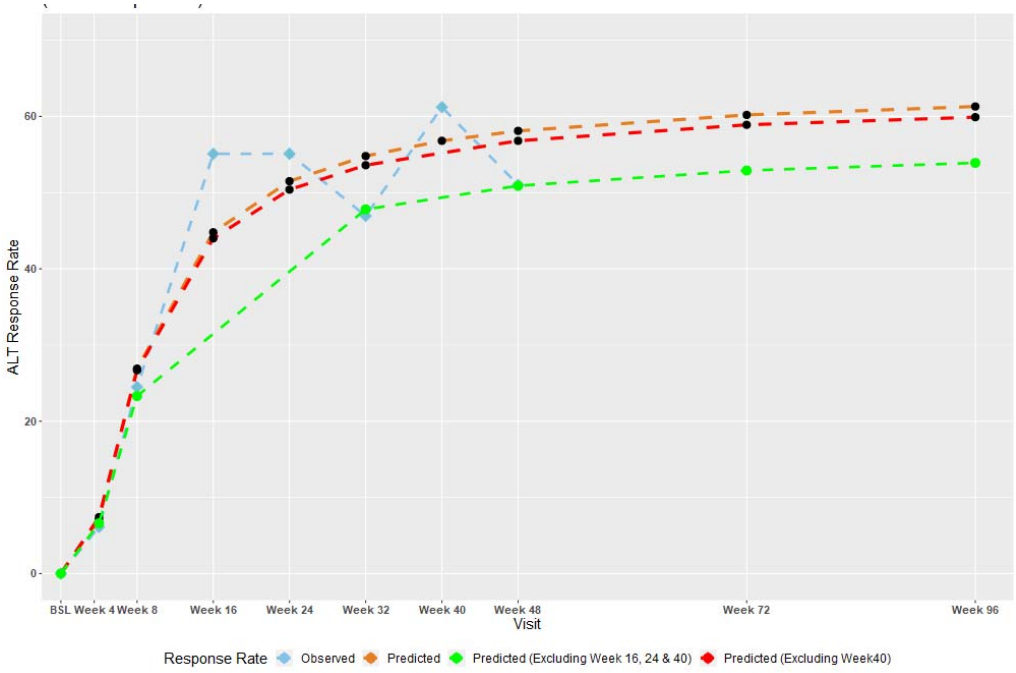
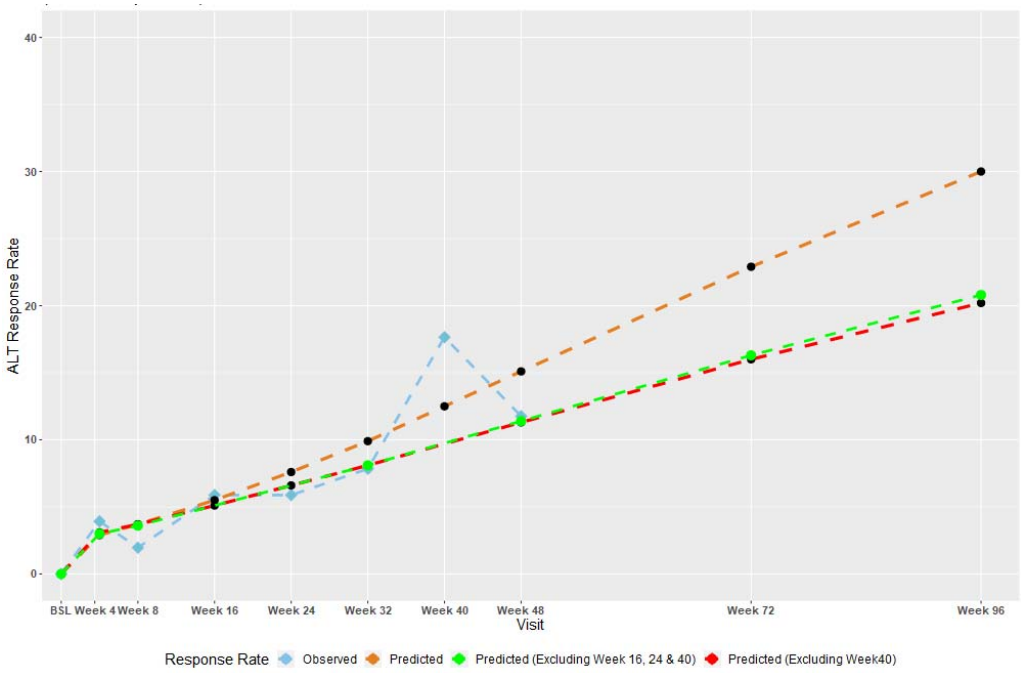


Figure 5. Observed vs predicted ALT response from EMAX models - BSC (overall population)



4.2.5.3 Estimation of disease progression

Patients were also allowed to transition between more granular states of disease progression in the model, within the general categories of response. The company undertook three separate steps in

order to estimate disease progression: 1) estimation of the natural history of disease for NRs; 2) estimation of hazard ratios (HRs) to model disease progression for PRs in relation to NRs; and 3) estimation of HRs to model disease progression for CRs in relation to NRs.

1) Natural history of disease

The company conducted a pragmatic literature search to identify natural history of disease data in HDV. Given the data limitations and heterogeneity in identified studies, the company decided to estimate the natural history of HDV progression based on publications comparing disease progression in HDV/HBV co-infected individuals versus HBV mono-infected patients. The EAG reports the values used by the company alongside the company's justification and the EAG's critique in the next subsection of the report and in Table 61 (Appendix 9.6).

The company also included an annual rate of spontaneous HbsAg seroclearance. The rate of HbsAg was assumed to be the same for all patients in the model (1.13%), and all patients with fibrosis (up to the F4 compensated cirrhosis stage) could experience a spontaneous clearance. The 24-week probability of seroclearance of 0.52% was used in the model and it was taken from a published meta-analysis. Patients who achieved HbsAg seroclearance were assumed to discontinue HDV treatment.

2) Estimation of HRs to model disease progression for PRs in relation to NRs

The company conducted a systematic literature review to identify cohort studies that reported the relationship of HDV RNA negativity vs positivity in terms of its impact on liver disease progression in chronic HDV patients. The company then undertook a meta-analysis, where HRs for specific liver disease progression events were estimated. The HRs obtained from the meta-analysis were applied to the TPs estimated for NRs and are reported below in Table 22.

Table 22. Disease progression treatment hazard ratios, partial responders

Health State		Hazard Ratio (Responder vs Non-Responder)	Source
From	To		
Fx	Fx+1	0.42	Company's meta-analysis
F2-F3	HCC	0.34	
F4	DCC	0.26	
	HCC	0.34	
	Death	0.22	

3) Estimation of HRs to model disease progression for CRs in relation to NRs

The company assumed that CRs have no progression compared to PRs or NRs. Therefore, the HRs for CRs were assumed to be zero in the company's updated model from the less severe to more severe fibrosis stages and from the F4 stage to the decompensated cirrhosis stage (as per Table 23). The same assumption of no disease progression was made from all the fibrosis stages to the HCC state, whereas the HR used to estimate the excess in mortality from the F4 (compensated cirrhosis) state was assumed to be the same as that used for PRs. Due to the company's assumption, CRs in the model never enter the DC state.

Table 23. Disease progression treatment hazard ratios, complete

Health State		Hazard Ratio (Responder vs Non-Responder)	Source
From	To		
Fx	Fx+1	0	Assumption and company's meta-analysis
F2-F3	HCC	0	
F4	DCC	0	
	HCC	0	
	Death	0.22	

In addition to the assumption that bulevirtide stops disease progression, the company also assumed that CRs in the F4 and F3 sates may experience a regression in liver fibrosis to the F3 and F2 states, respectively. The company based the assumption of regression from the F4 state on the Farci *et al*. 2004 study[36], which looked at HDV patients responding to PEG-IFN therapy, and reported regression in four out of six patients with sustained biochemical response; and the assumption of regression from the F3 state on Marcellin *et al*. 2013[37], which reported regression of cirrhosis for HBV mono-infected patients who experienced viral suppression while on treatment. The annual transition rates used in the model for fibrosis regression among combined responders are reported in Table 24.

Table 24. Fibrosis regression for complete responders (regardless of treatment arm)

Health States		Annual Transition Probabilities	24-week cycle probability	Source
From	To			
CC (F4)	NC (F3)	8.8%	4.17%	Farci *et al*. 2004 (103)
F3	F2	13.3%	6.37%	Marcellin *et al*. 2013 (102)

4.2.5.3.1 EAG critique of estimation of disease progression

1) Natural history of disease

Overall, the EAG is concerned that the company did not provide a robust justification for why the sources used in the model to estimate the natural history of disease were selected. Given the scarce literature around HDV, the EAG understand the company's choice to use estimates from the natural history of HBV mono-infected patients to then adjust the risk of outcomes for HDV/HBV co-infected patients. Nonetheless, the EAG notes that there seems to be more estimates available directly from HDV literature than those used by the company. The EAG also notes that the HBV evidence base is extensive, and that the company's approach to selecting TPs to estimate the natural history of disease does not appear to have been systematic. The EAG also notes that there have been no previous TAs conducted in CHD, therefore, there is no precedent for previously committee-accepted TPs in the economic analysis in this disease area.

Due to time limitations, the EAG could not conduct its own systematic literature review, or any methods of data synthesis, however, in Table 61 in Appendix 9.6, the EAG notes some of the company's discrepancies in parameter choices and suggests alternative sources (mainly out of the sources already identified by the company). For example, where sources were available to directly estimate the natural history of disease in HDV patients, the EAG suggests using these, instead of using estimates for HBV and then adjusting the latter.

Probability of HCC

On the relationship between cirrhosis and HCC, the Alfaiate *et al*. 2020[38] study recognises that most HCC events occur at late stages of infection and that cirrhosis is the most important risk factor for HCC. The authors add that long-term follow-up studies show that most HDV-associated HCCs arise in

cirrhotic livers, suggesting that cirrhosis may also be the main carcinogenic driver in these patients. Nonetheless, the authors also acknowledge the fact that HDV does not integrate into the host cell genome and thus has a direct oncogenic potential, with experimental data supporting a potential hepatocarcinogenic role of HDV antigens and a specific molecular signature of HDV-associated HCC. The authors explain that the demonstration of a potential specific oncogenic role of HDV would only be possible using robust cohort study designs where cirrhosis was no longer a confounder. The authors further acknowledge one cohort study (Kushner *et al*.[3]) which accounted for cirrhosis as a confounder and found a statistically significant HR of 2.1 for HCC in HDV-infected patients, independently of cirrhosis (which itself had a significant HR of 5.2 for HCC). Therefore, the EAG agrees with the company's assumption that patients in all F-stages are likely to experience HCC (an assumption which has also been validated by the EAG's clinical expert), however, there seems to be a lack of robust evidence to estimate the relationship between the different F-stages on the likelihood of HCC.

The company used the Hsu *et al*. 2002[39] study to estimate the probability of F2 patients developing HC; the Dienstag *et al*. 2011[40] paper to estimate the probability of F3 patients developing HCC; and the Bermingham *et al.* 2016[41] study to estimate the probability of F4 patients developing HCC.

The EAG does not agree with the use of any of these sources to estimate HCC in the model (see Table 61 in Appendix 9.6 for more details) as there were two available alternative sources where the HCC estimates for patients with HDV could have been directly taken from the right population, instead of being taken from HBV populations. These were the Fattovich *et al*. 2000 and the Romeo *et al*. 2009 studies.[8,2]

The Fattovich *et al*. 2000 study included untreated HDV patients, with compensated cirrhosis at baseline and reported a 10-year probability of HCC (adjusted for age and HDV status) of 25% which translates into an annual probability of 2.84%.[8]

The Romeo *et al*. 2009 study analysed data from 299 patients who had been HDV positive for at least 6 months admitted from 1978 to 2006 in Italy. Ninety patients were treated with interferon, 62 with corticosteroids, and 12 with nucleoside analogues; 135 received no therapy. The information provided for the non-treated patients was scarcer than for the rest of the patients, thus the probability of HCC in patients with compensated cirrhosis of 5.61% annually was for the entire group of untreated (45%) and treated (55%) patients.

Given the available evidence discussed above, the EAG considers that a more robust method for estimating the probability of HCC for the F2 and the F3 states would be to use the probability of HCC from the compensated cirrhosis stage from either the Fattovich *et al*. 2000 or the Romeo *et al*. 2009 studies, and work backwards to calculate the probability of HCC in lower F-stages by using the HR from Kushner[3] of 5.2. The HR can be applied to the Fattovich *et al*. 2000 or the Romeo *et al*. 2009 estimate in order to calculate the probability of HCC from the F3 fibrosis state.[8,2]

The EAG does not consider that enough evidence exists to directly model a TP between the F2 state and HCC, however, hypothesises that the same relationship observed between compensated cirrhosis and F3 states (HR of 5.2) could be observed between the F3 and the less severe stages of fibrosis.

The EAG estimated the two sets of TPs (based on Fattovich *et al*. 2000 and Romeo *et al*. 2009) for the F4 to the HCC state, and then applied the HR of 5.2 to estimate the TP between F3 and HCC. To the latter, the EAG applied the HR of 5.2 again to estimate the TP between F2 and HCC. These values (Table 25) have been presented to the EAG's clinical experts for validation. The clinical experts considered that the values based on Romeo were more representative of clinical practice. The EAG presents the results of including these estimates in the model in Section 6.3.

Table 25. EAG's estimation of the probability of HCC

Health State		Transition probability (per annum)	Source
From	**To**		
Non-responder	HCC	-	Romeo[2] and Kushner[3]
F2		0.04%	
F3		1.10%	
F4		5.61%	
Non-responder		-	Fattovich[8] and Kushner[3]
F2		0.01%	
F3		0.55%	
F4		2.84%	

Progression of fibrosis

Overall, the literature available for HDV patients reported lower rates of fibrosis (and cirrhosis) progression than the company's final estimates calculated from the HBV literature and then adjusted with multipliers for co-infected patients. Therefore, even though the EAG's preference is to use data directly estimated in the relevant population, the EAG also recommends that the committee seek

expert clinical opinion to validate the clinical plausibility of the estimates proposed by the company and the EAG.

The company reported taking the 5.3% probability of transition between F-states from Bermingham et al. 2016[41], which in its turn, reported taking the estimate from Fattovich 2003[42]. In the latter, the cumulative incidence of cirrhosis in people with predominantly HBeAg positive CHB was reported to range from 8% to 20% over a five-year period. The study reports taking the upper limit of the range and converting it into an annual probability of 5.3%.

The company then multiplied the 5.3% estimate by threefold as per Da *et al.* 2018[43], a literature review of the natural history of HDV (among other aspects of the disease) which concluded that patients co-infected with chronic HBV/HDV have a threefold risk of cirrhosis progression compared with HBV alone. The company therefore used a TP of 15.11% between F-states in the model.

The EAG is unclear on how 20% over a 5-year period translated into a 5.3% probability and considers this should have translated into a 4.36% probability instead. More importantly, the population in Fattovich 2003[42] was predominantly HBeAg positive, whereas 90% of patients in the MYR 301 trial were HBsAg negative. Crucially, the Romeo *et al*. 2009 study on HDV positive patients included estimates of progression from the different METAVIR stages to the compensated cirrhosis stage.[2]

Romeo *et al*. 2009 reported that out of the 135 untreated patients, only 16 (0.8% of patients annually) developed cirrhosis during the 16.5 years follow-up period. This compares to the 15.1% used by the company from every fibrosis stage. The study also provided the annual probability of patients going from specific F-stages to the cirrhotic (F4) stage in the entire population (i.e. treated and untreated patients), where: F0 and F1 patients at baseline had a probability of 2.4% of becoming F4 patients; F2 patients had a probability of 6.93% of becoming F4 patients; and F3 patients had a probability of 7.18% of transitioning to F4.[2]

In order to estimate the probability of progression from F4 to a decompensated cirrhosis stage, the company used data from Dakin 2010[44] (a cost-effectiveness study in CHB) to obtain the annual transition probability of 5.0% to then increase it to represent faster progression in HDV patients using the 2.2 multiplier from Fattovich *et al*. 2000. The EAG notes the lack of justification provided by the company to use the Fattovich study to derive a multiplier to be applied to a CHB estimate, when the study itself provided a 10-year probability of decompensated cirrhosis of 25% (which

translates into an annual probability of 2.84%) for untreated HDV patients with compensated cirrhosis at baseline.

The estimate from Fattovich *et al*. of 2.84% compares to 10.67% assumed by the company and 14.67% estimated in Romeo *et al*. 2009.[2] The EAG acknowledges that the estimate from Fattovich is low, especially when compared to Romeo given that patients in Fattovich were untreated and Romeo included treated patients. The EAG's clinical experts advised that HDV is a rapidly progressing disease and indicated that the values reported in Fattovich were too low. In Table 61 (Appendix 9.6) the EAG provides the estimates used by the company together with the values used from Romeo *et al.*[2] Results from including these estimates in the model are provided in Section 6.3.

The EAG caveats the Romeo estimates by the fact that they do not provide the probability of patients transitioning to the immediate next F-stage, but instead to the F4 stage, however, these estimates provide an alternative to assuming a constant progression in the F2 and in the F3 states.

Table 26. Disease progression treatment hazard ratios, partial responders

Health State		Company's base case	Romeo et al[2]
From	To		
F2	F3	15%	6.93%
F3	F4	15%	7.18%
F4	DCC	10.67%	14.67%

2) Estimation of HRs to model disease progression for PRs in relation to NRs

The EAG is concerned that the studies included in the company's meta-analysis did not restrict response to virological response (i.e., did not match the company's definition of PR in the model), but instead included patients with both virologic and biochemical response. Therefore, it is likely that the HRs estimated in the company's meta-analysis overestimate the effect of being a PR. Nonetheless, the EAG conducted an exploratory scenario analysis where the HRs for PRs were assumed to be doubled in relation to HRs estimated in the company's meta-analysis (i.e., the EAG assumed half of the effect estimated by the company) and the impact on the final ICER was limited (less than £1,500 per QALY gained).

The EAG also notes that the HRs from the meta-analysis were varied by +/- 20% in the company's probabilistic sensitivity analysis (PSA). However, the 95% confidence intervals were available from

the meta-analysis conducted by the company. Therefore, during clarification, the EAG asked that the company replaced the confidence intervals used in the PSA by the ones provided by the meta-analysis, which the company incorporated in their updated model.

3) Estimation of HRs to model disease progression for CRs in relation to NRs

Being a CR in the model generates benefits through patients having a 0% probability of progressing from the F2 to the F3; the F3 to the F4 states; as well as progressing from the F4 state to a decompensated cirrhosis state. Additionally, being a CR (vs a PR and a NR) in the F2 to F4 categories is also associated with a 0% probability of HCC (Table 27).

The EAG's clinical experts agreed with the company's assumption that CRs have no progression in their fibrosis when compared to NRs, however, that it would be too optimistic to assume that CRs do not have a chance of developing HCC, given that HCC is related to fibrosis staging as well as HDV presence (as discussed in the natural history of disease section above). Furthermore, the Alfaiate study also suggests that HCC is likely to occur even in patients considered to be responders, thus, while CRs might have a lower chance of experiencing HCC compared to NRs, it is not plausible to assume that CRs would not develop HCC.

Therefore, the EAG considers that the benefits associated with being a CR (and thus bulevirtide) are potentially overestimated in the model, given the company's assumption that being a CR is associated with a 0% probability of disease progression through the F-states (therefore a higher proportion of patients remain in the lower F-stages) on top of CRs in the lower F-states also being assumed to experience a 0% probability of HCC. The EAG conducted a scenario analysis where it was assumed that CRs have the same probability as PRs (which is lower than the probability of NRs) of developing HCC. Results are presented in Section 6.3.

Table 27. Probability of transition to the HCC state in the company's base case model

Health State		Transition probability (per 24-week cycle)	Source
From	To		
Responder	HCC	-	Assumption
F2		0%	
F3		0%	
F4		0%	
Decompensated cirrhosis		3.69%	
Partial responder		-	

F2		0.22%	Company's meta-analysis
F3		0.46%	
F4		1.02%	
Decompensated cirrhosis		3.69%	
Non-responder		-	Natural history of disease
F2		0.64%	
F3		1.33%	
F4		2.93%	
Decompensated cirrhosis		3.69%	

The EAG's experts also agreed that CRs could experience fibrosis regression. During clarification, the EAG noted that the company assumed that fibrosis regression could start occurring within the first 24 weeks of treatment (i.e. first model cycle), however, the Farci *et al*. 2004 study (used by the company to estimate the probability of fibrosis regression) reported that fibrosis regression did not start occurring until at least 72 weeks after treatment initiation in the study. As a result, the EAG asked that the company changed the assumption in the model to reflect that fibrosis regression could only start occurring from cycle 4 onwards (i.e. 96 weeks) in the model. The company included a scenario analysis to reflect the EAG's request which increased the ICER from £40,562 to £40,901 per QALY gained.

4.2.6 Mortality

All-cause mortality was applied using a background mortality rate in the model and is sourced from national life tables from the Office for National Statistics.

Additionally, liver-related excess mortality was applied from the F4 state onwards to capture the excess mortality risk associated with liver disease (as reported in Table 28). For CRs and PRs in the F4 state, there was a benefit in survival compared to NRs, however, once patients progressed from the F4 state, liver-excess mortality was assumed to be the same regardless of response status.

Table 28. Excess mortality in addition to general population mortality associated with liver disease in the model

Health State		Annual transition probability	Source
From	To		
Responder	Dead	-	Assumption
F2 and F3		0%	
F4		1.63%	
Decompensated cirrhosis		Same as NR	

HCC		Same as NR	
LT		Same as NR	
PLT		Same as NR	
Partial responder		-	Company's meta-analysis (HR of 0.22)
F2 and F3		0%	
F4		1.63%	
Decompensated cirrhosis		Same as NR	
HCC		Same as NR	
LT		Same as NR	
PLT		Same as NR	
Non-responder		-	Natural history of disease section
F2 and F3		0%	
F4		7.26%	
Decompensated cirrhosis		15.60%	
HCC		56.00%	
LT		21.00%	
PLT		5.70%	

4.2.6.1 EAG critique

In addition to the issues raised in relation to the company's meta-analysis in Section 4.2.5.3.1, the EAG notes the following issues regarding the 5 studies included in the estimation of the excess of mortality for HDV positive patients: 1 of the studies did not specify the cirrhotic status of patients at baseline (or throughout the study) and was conducted in HIV/HBV coinfected patients which as acknowledged in the study, "*has been associated with a higher incidence of hepatic flares and decompensation as well as an increased mortality*"(Beguelin *et al*.[7]); 1 of the studies included survival for patients with HDV genotype 5 vs HDV genotype 1 (and the EAG cannot see how different types of genotype would be a proxy for HDV RNA negativity) (Spaan[35]); 1 study included the impact of HDV RNA negativity on the probability of death and liver transplant combined (Kamal[45]); and the remaining 2 studies included a mix of patients with DC and CC and did not specify the cirrhotic stage of patients who died (Roulot[46] and Yurdaydin[5]).

Therefore, the EAG considers that: the HR of 0.22 is likely to be underestimated, as the Beguelin[7] and Kamal[45] studies reported the lowest HRs of 0.13 and 0.14, respectively; and that it cannot be ascertained if the HR should be applied in the F4 or the DC (or potentially a combination) categories of the model. Nonetheless, the EAG tested using the highest HR from the meta-analysis (0.37 HR

from the individual study of Spaan[35]) in the model and concluded that the impact on the final ICER is negligible.

Furthermore, the company assumed that liver-related death in the CC state was higher for HDV patients vs HBV, while liver-related death associated with DC; HCC; LT; and PLT was assumed to be the same across conditions. When asked by the EAG to justify its choice, the company reported that clinical expert opinion provided to the company was that after patients progress to DC; HCC, or LT the risk of liver-related death would be the same for HDV coinfection vs HBV mono-infection. The EAG recommends that the company's assumption is validated by the committee using clinical expert opinion.

Finally, the company assumed that patients in the F2 and F3 states have the same mortality as the general population (regardless of response status). The EAG's clinical expert reflected that this assumption is clinically implausible as all patients in the model have hepatitis B (thus should experience an increased mortality). The EAG asked the company to adjust the mortality in the model to reflect clinical plausibility, however the company replied that prior models including HBV patients with non-cirrhotic disease (including those with F2 and F3 disease), have assumed that excess mortality is either low or zero. The company reports that in TA173 the model for tenofovir disoproxil fumarate, patients with viral suppression were assumed to have a rate of excess mortality associated with viral suppression of 0.35%, while in TA153, only transitions to liver-related mortality were considered from DC or HCC, with excess mortality due to liver disease not considered for patients with compensated cirrhosis (F4) nor patients with DC. The EAG increased background mortality in the model by 0.35% and the impact on the final ICER was negligible.

4.2.7 Adverse events

The company included grade 3 treatment emergent adverse events (AEs) in the economic analysis that occurred in more than one patient in both the delayed treatment and bulevirtide 2 mg arms from MYR 301. In the CS, the company notes that no grade 4 AEs were experienced by any patients in MYR 301. Table 29 presents the AEs included in the economic model. AEs for the delayed treatment arm in MYR 301 were assumed for the BSC in the economic model.

Table 29. Adverse events included in the model

Adverse event	Bulevirtide 2 mg	Best supportive care
Neutropenia	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]

Leukopenia	[redacted]	[redacted]

Abbreviations: mg, milligram.

The incidence of AEs for each arm of the economic model was used to estimate a disutility impact as well as the cost of treatment related to each AE. The company assumed that the total disutility and costs of AEs occurred in the first model cycle. Further detail on AE disutility and costs can be found in Section 4.2.8 and 4.2.9.

4.2.7.1 EAG critique

The EAG considers that the company's approach to selecting and implementing treatment emergent AEs in the economic model is appropriate. Furthermore, the EAG's clinical experts considered that the lower 2 mg dose of bulevirtide mitigates against the emergence of AEs that were seen with the higher 10 mg dose from MYR 301. However, the EAG notes that AEs are not a primary driver of cost-effectiveness for bulevirtide and any changes to the incidence has relatively little impact on the ICER.

4.2.8 Health-related quality of life

In the economic model, QALYs accrued by the patient cohort in each model cycle are dependent on the utility attributable to each health state, a utility gain associated with being a CR to treatment, and the partial loss of utility due to adverse events. The details of each are given in the following subsections.

4.2.8.1 Health state utility values

In the economic model, QALYs accrued by the patient cohort in each model cycle are dependent on the utility attributable to each health state, a utility gain associated with being a CR to treatment, and the partial loss of utility due to adverse events. The details of each are given in the following subsections.

4.2.8.2 Health state utility values

EQ-5D-3L data were collected in MYR 301, however the company considered it lacked face validity given that a descriptive analysis of the data showed there was no numerical difference in utility values between cirrhotic and non-cirrhotic patients at baseline.[47] Moreover, the company stated that key symptoms of CHD such as fatigue, nausea and vomiting are not well reflected in the EQ-5D-3L descriptive system. As mentioned in Section 4.1, the company did not identify any suitable CHD-specific health state utility data in the SLR that could be used in the economic model. Thus, a

separate SLR and meta-analysis of utility values for CHB and chronic HCV was conducted, as the company's clinical experts advised that these conditions are suitable proxies for CHD.

Consequently, health state utility values (HSUVs) in the company's analysis were informed by a meta-analysis of health state utilities for CHB, whereas the utility data for chronic HCV were explored in a scenario. Table 30 presents the HSUVs for the base case and scenarios included in the economic model.

Even though the company deemed the MYR 301 utility data unsuitable for the base case, the HSUV data for the F2 to F4 health states were explored in a scenario, presented in Table 30. In MYR 301, EQ-5D-3L data were collected from the full analysis set (FAS) population at baseline, week 24 and week 48. The mean baseline utility value of 0.81 from the company's descriptive analysis of the MYR 301 EQ-5D-3L data was used in the scenario for the F2 to F4 health states.

Table 30. Health state utility values included in the model

Health state	Utility value		
	Base case - CHB meta-analysis[48]	Scenario - chronic HCV meta-analysis[48]	Scenario - MYR 301
F2	0.85	0.85	0.81
F3	0.85	0.85	0.81
F4 (compensated cirrhosis)	0.76	0.72	0.81
DCC	0.46	0.70	0.46*
HCC	0.52	0.69	0.52*
LT	0.57	0.46	0.57*
PT	0.67	0.80	0.67*

Abbreviations: CHB, chronic hepatitis B, DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; HCV, hepatitis C virus

*Utility values for these health states are based on the company's CHB meta-analysis[48]

4.2.8.3 Complete responder utility gain

In the base case, the company included a CR utility gain to capture the benefit of achieving the composite outcome of virologic response (HDV-RNA undetectability or ≥2-log10 decline) and ALT normalisation. The company considered that the MYR 301 data provided the best estimate for the gain in utility associated with a complete response for patients with CHD.

The company estimated the CR utility gain using a Tobit regression model, fitted to the 48-week pooled utility data from the delayed treatment and bulevirtide 2mg arms of the MYR 301 trial, as no statistically significant difference was found between the trial arms.

For the final Tobit model, the company stated that variables were selected based on internal discussions and advice from clinical experts. The variables included in the final Tobit model were liver cirrhosis status at baseline and responder status at week 48 (see Table 31). Based on the Tobit regression, the coefficient of [redacted] ([redacted]) for CR was used to estimate the utility gain. The utility gain was applied in addition to the HSUVs for the F2 to F4 health states for patients who achieve a complete response.

Table 31. Tobit regression analysis of 48-week MYR 301 utility data (Table 52 of the CS)

	Estimate	95% CI	p-value
Intercept	[redacted]	[redacted]	[redacted]
Baseline EQ-5D	[redacted]	[redacted]	[redacted]
Liver cirrhosis at baseline	[redacted]	[redacted]	[redacted]
Complete responder	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval.

4.2.8.4 Adverse event related disutilities

In the base case, the company included the impact of AEs on quality of life. Disutilities associated with AEs were applied as a one-time QALY decrement in the first model cycle, calculated based on the proportion of patients in each treatment arm who experienced each AE (Table 29, Section 4.2.7) and the company's estimate of the disutility associated with any active grade 3 AE. The utility decrements for each AE are presented in Table 32.

In their clarification response, the company stated that a targeted literature search was performed to identify relevant disutility values for each AE as none were identified in the HRQoL search or from previous NICE appraisals in hepatitis B. Additionally, the company provided a scenario where AE related disutilities were excluded from the analysis and this had minimal impact on the ICER (see Section 5.1.2.3).

Table 32. AE related utility decrements included in the economic model (Table 57 of the CS)

Adverse Event	Utility decrement	Source
Neutropenia	0.163	Tolley *et al.* 2013[49]
Thrombocytopenia	0.061	Sullivan *et al.* 2011[50] (assumed same as 'other blood disease')
Leukopenia	0.061	Sullivan *et al.* 2011[50] (assumed same as 'other blood disease')

Abbreviations: AE, adverse event; CS, company submission

4.2.8.5 EAG critique

The EAG disagrees with the company's view that the MYR 301 utility data for cirrhotic and non-cirrhotic patients are not appropriate for use in the economic model and notes the inconsistency in the company's approach which implies that the data are suitable to estimate the gain in utility for CRs. As per the NICE methods guide, measurement of changes in health-related quality of life should be obtained directly from patients.[51] Furthermore, the company's argument that the EQ-5D data from MYR 301 lacks validity because the baseline utility value for patients is the same irrespective of cirrhosis status contradicts a statement made by the company in the CS (page 115), reporting that, "*Patients progress through stages of fibrosis before developing cirrhosis. Cirrhotic patients remain asymptomatic or with limited symptoms (i.e., CC) before developing DCC*".

Crucially, the EAG consulted with its clinical experts to understand the impact of cirrhosis on patients' quality of life and was advised that patients in the F4 state are generally asymptomatic, thus making it unlikely that F4 patients experience a difference in quality of life compared with non-cirrhotic patients. Therefore, the EAG considers that the utility data from MYR 301 should be used for the F2 to F4 health states. The EAG notes that the company's scenario using the MYR 301 utility estimate of 0.81 is based on a mean baseline utility, whereas a Tobit regression was used to estimate the utility gain for CRs.

The CR utility gain estimated from the Tobit model is a primary driver of cost-effectiveness. The EAG's clinical experts advised that response to treatment is likely to have the most significant impact on a patient's HRQoL. As such, the EAG considers that the inclusion of a utility gain for CR is appropriate.

The EAG was concerned that the company's approach to choosing the variables to be included in the Tobit model was not systematic, therefore, during clarification the EAG asked that the company

provided the outcomes of the stepwise approach used to assess the statistical significance of each independent variable in the model. The company replied that a stepwise approach had not been taken and instead that variables were selected based on internal discussion and clinical expert opinion. It is, therefore, not surprising that all of the final variables included in the Tobit model were not statistically significant (see Table 31). It should be noted that 49% of data on METAVIR staging at baseline was missing in MYR 301, therefore, the results of the Tobit model pertaining to baseline cirrhosis status need to be interpreted with caution.

The Tobit model produced a 0.81 utility value for NRs for the F2-F4 states, which is similar to that observed in the baseline descriptive mean utility for all patients at baseline in MYR 301. Given the clinical expert view that responders are expected to have a gain in their utility regardless of which fibrosis state they are in, the EAG considers that the inclusion of the non-statistically significant coefficient from the Tobit model for response is not unreasonable. However, the EAG acknowledges that results from the Tobit model are not statistically significant, and thus should be interpreted with caution.

In Section 6.2, the EAG reports the results of the scenario analysis where the utility gain for responders was excluded and using the MYR 301 baseline utility value of 0.81 for the F2 to F4 health states.

For the DC, HCC, LT and PLT health states, utilities were derived from the company's meta-analysis of CHB utility values. The company only provided the meta-analysis to the EAG a week before the deadline of the EAG's report, therefore, the EAG could not fully validate the analysis. Nonetheless, the EAG considers that the meta-analysis is generally fine despite an apparent lack of clarity for the criteria used to include studies in the final meta-analysis estimates.

The EAG compared the company's utility estimates for the DC, HCC, LT and PLT health states against previous TAs for CHB (TA173 and TA153), presented in Table 33 given that the EAG's clinical experts agreed that utility values for the CHB population can be considered a suitable proxy for the CHD population. Compared to previous TAs, the company's meta-analysis estimated higher utility values for the DC and the HCC health states, but much lower values for the LT and PLT states.

The EAG notes that the source of utility values from TA173[52] and TA153[53] are from the same multinational study[54], however TA173 uses data from the UK cohort[55], whereas TA153 uses data from the entire study. The EAG considers that utility values from the company's meta-analysis may

potentially be more robust as they are not reliant on a single study and include studies published after the release of TA153 and TA173 (over 13 years ago). However, the EAG considers that the utility value for the PLT health state is too low in comparison with the F-stages utility values used by the company (0.85) or proposed by the EAG (0.81), especially as this is the permanent health state for patients whose liver transplant was successful.

As such, the EAG ran two scenarios in combination with using the EAG-preferred utility value of 0.81 for the F-stages (and [redacted] for CRs) – one where patients in the PLT state were assumed to return to their original utility value before they progressed from the F-stages; and another where the relative difference from TA173 between the CC state the DC, HCC, LT, and PLT was applied to the EAG's preferred baseline utility value of 0.81 from MYR 301. The results of the TA173 adjusted utility values had a minimal impact on the ICER (see Section 6.3)

Table 33. Comparison of health state utility values from previous TAs and the company base case values

Health state	Tenofovir (TA173[52])	Entecavir (TA153[53])	Company base case - Meta-analysis of CHB utility values
DCC	0.36	0.36	0.46
HCC	0.46	0.42	0.52
Liver transplant (LT)	0.71	0.69	0.57
Post liver transplant (PLT)	0.82	0.82	0.67

Abbreviations: CHB, chronic hepatitis B; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; TA, technology assessment.

In the company's base case, age-related utility decrements were not included. The NICE methods guide states that, "*If baseline utility values are extrapolated over long time horizons, they should be adjusted to reflect decreases in health-related quality of life seen in the general population*".[51] The EAG considers this to be a significant omission as the mean age in the model is 35 years and the model time horizon is lifetime. During the clarification stage, the company provided a scenario where age-related utility decrements were included in the analysis, but they did not justify why this was not included in their base case. Inclusion of age-related utility decrements increased the ICER from £40,562 to £43,898. As it is methodologically appropriate to adjust utilities for age, the EAG has included age-related utility decrements in its base case, presented in Section 6.2.

4.2.10 Resource use and costs

The costs included in the economic model are listed below and discussed in detail in the following sub-sections:

- Drug acquisition costs (Section 4.2.8.6);
- Monitoring costs (Section 4.2.8.9);
- Health state unit costs (Section 4.2.8.10); and
- Adverse event costs (Section 4.2.10.11).

4.2.8.6 Drug acquisition costs

Bulevirtide is given as a daily 2 mg subcutaneous (SC) injection, self-administered by patients. The list price per pack of 30 vials of 2 mg powder for solution for injection is [redacted]. A patient access scheme (PAS) discount of [redacted] is available for bulevirtide, resulting in a discounted pack price of [redacted] and a cost per vial of [redacted]. The total discounted cost of bulevirtide per 24-week cycle is [redacted]. In the company's clarification response, it was confirmed that the cost to provide training to patients on how to self-administer bulevirtide would be borne by the company and consequently this cost has not been included in the economic model.

No drug acquisition costs were applied to the BSC arm as no active treatments are currently recommended for patients with CHD. However, the cost of monitoring for BSC patients was considered in the economic model and is detailed further in Section 4.2.8.9.

4.2.8.7 Treatment discontinuation

The SmPC for bulevirtide states that, "*treatment should be continued as long as associated with clinical benefit*" given that the optimal duration for treatment is unknown. In the economic model, the following bulevirtide treatment stopping rules were implemented:

- No complete response to treatment at week 48 (PRs were allowed to continue treatment);
- No complete response by week 72 (remaining PRs were assumed to become NRs and stop treatment);
- Responders experiencing spontaneous clearance (HbsAg seroclearance);
- Disease progression to DCC, HCC; LT and PLT;
- Treatment discontinuation based on treatment withdrawal for any other reason in MYR 301. In the trial, one patient out of 49 (2.04%) in the bulevirtide 2 mg arm discontinued treatment

thus, the company converted the background treatment discontinuation probability into a 24-week probability (1.03%) to be used in the model.

4.2.8.8 EAG critique

The EAG is concerned about the company's approach to modelling treatment discontinuation given the lack of clarity around treatment stopping rules in MYR 301 and the fact that bulevirtide treatment groups are scheduled to continue treatment up to 144 weeks in the trial follow-up period.

In the economic model, the company assumed that non-responders to treatment at week 48 discontinue treatment, however, the company did not provide a clear justification for this assumption and the EAG is unclear if 48 weeks was chosen due to this being the same data cut-off period available for MYR 301; or for any other reason such as the existing EASL guidelines, which strongly recommend treatment with PEG-IFN for at least 48 weeks in HDV-HBV coinfected patients with compensated liver disease, irrespective of on-treatment response pattern if well-tolerated. Crucially, the EAG notes that this aspect of the economic model will need careful re-assessment when the 96-week follow-up data are available for MYR 301. When more mature data are available, duration of treatment and time to response in the trial will need to be investigated, as it might be that, for example, NRs at week 48 continued treatment and became responders later in the trial.

The SmPC for bulevirtide states that, "*The optimal treatment duration is unknown. Treatment should be continued as long as associated with clinical benefit*". As such, the EAG agrees with the company's assumption that PRs who have not achieved a complete response continue treatment up to week 72, however, notes that in MYR 301, treatment is likely to have carried on for a longer period of time for these patients. As discussed in Section 4.2.5, the EAG considers the extrapolation of response data beyond week 48 to be inappropriate, which is only reinforced by the uncertainty around assumptions made for treatment discontinuation after week 48 in the model.

Finally, clinical expert opinion provided to the EAG was not consistent with regards to stopping treatment upon disease progression. While one expert agreed that due to lack of trial evidence on treating patients with DC, treatment would be stopped upon decompensation; the other expert stated that treatment would be continued if patients developed DC or HCC. The latter is consistent with TA173 (tenofovir disoproxil for the treatment of chronic hepatitis B). Regardless, the SmPC for bulevirtide states that bulevirtide is not indicated for patients with DC. Therefore, the EAG included

a scenario analysis in the model where responders in the HCC state were allowed to continue treatment with bulevirtide. The results of the EAG's scenario are reported in Section 6.3.

4.2.8.9 Monitoring costs

For patients in the F2 to F4 states of the model, monitoring costs were applied and varied by treatment arm and cirrhosis status. Table 34 presents the monitoring resource use for the bulevirtide and BSC arms of the model. For patients on bulevirtide, the company assumed different monitoring resource use for treatment initiation and throughout treatment, with both being stratified by cirrhosis status. For BSC and bulevirtide patients who have discontinued treatment, monitoring resource use varied by cirrhosis status only. Table 35 presents the unit costs of monitoring (derived from NHS Reference Costs 2019-2020[33]) and Table 36 presents the overall cost of monitoring for each arm of the model, by cirrhosis status. The EAG found a calculation referencing error in the model for the monitoring cost of BSC patients who are non-cirrhotic, which resulted in a differential cost based on treatment status (which is not relevant for this arm of the model). The EAG corrected this error and updated results are presented in Section 6.1.

Table 34. Monitoring resource use (Table 60 and Table 61 of the CS)

Resource	Bulevirtide treatment initiation (one-off)		During bulevirtide treatment (annual)		Off bulevirtide treatment & BSC	
	Non-cirrhotic	Compensated cirrhosis	Non-cirrhotic	Compensated cirrhosis	Non-cirrhotic	Compensated cirrhosis
Hepatologist visit	1	2	3	4	2	2
Outpatient visit	1	1	1	2	2	2
Fibroscan®	1	1	1	1	1	1
Liver biopsy	1	0	0	0	0	0
HBV DNA test	1	1	2	2	2	2
HDV-RNA test	1	1	2	2	1	1
Liver enzyme test	1	2	2	3	2	2
Complete blood count	1	2	2	3	2	2
TSH test	0	0	0	0	0	0
Renal function test	1	2	2	3	2	2
Bilirubin Test/GGT/ALP test	1	2	2	3	2	2

Ultrasound for HCC screening and surveillance	1	1	2	1	2	2
Protime/INR	1	2	1	3	1	2
anti-HDV IgG	1	1	0	0	0	0
HBsAg	1	1	1	1	1	1
HCV Ab	1	1	0	0	0	0
HIV Ab	1	1	0	0	0	0
Hepatis A IgG	1	1	0	0	0	0
Alpha-feto Protein	1	1	2	2	2	2

Abbreviations: Ab, antibody; ALP, alkaline Phosphatase; BSC, best supportive care; DNA, deoxyribonucleic acid; GGT, gamma-glutamyl transferase; HBsAg, Hepatitis B surface antigen; HBV, hepatitis B virus; HCC; hepatocellular carcinoma; HCV, hepatitis C virus; HDV, hepatitis D virus; HIV, human immunodeficiency virus; INR, international normalized ratio; RNA, ribonucleic acid; TSH, thyroid stimulating hormone.

Table 35. Monitoring resource use unit costs (Table 62 of the CS)

Resource use item	Unit cost	Source
Hepatologist visit	£88.20	Non-admitted face-to-face attendance, consultant led hepatology, currency code: WF01C, service code:306. NHS reference costs 2019-20[33]
Outpatient visit	£88.20	Non-admitted face-to-face attendance, consultant led hepatology, currency code: WF01C, service code:306. NHS reference costs 2019-20[33]
Fibroscan®	£43.93	Ultrasound elastography, currency code: RD48Z, outpatient imaging, NHS reference costs 2019-20[33]
Liver biopsy	£80.51*	Ultrasound elastography, currency code: RD48Z, outpatient imaging; histopathology and histology, currency code: DAPS02, NHS reference costs 2019-20[33]
HBV DNA test	£1.20	DAPS04, Clinical biochemistry, NHS reference costs 2019-20[33]
HDV-RNA test		
Liver enzyme test		
Complete blood count	£3.67*	DAPS08, phlebotomy, NHS reference costs 2019-20[33]
TSH test	£1.20	DAPS04, Clinical biochemistry, NHS reference costs 2019-20[33]
Renal function test		
Bilirubin test/GGT/ALP test		
Ultrasound for HCC screening and surveillance	£45.21	Weighted average of codes RD40Z-RD43Z, Ultrasound scan with duration of less than 20 mins or 20 mins and over, with and without contrast, NHS reference costs 2019-20[33]
Protime/INR	£2.53	DAPS05, Haematology, NHS reference costs 2019-20[33]
anti-HDV IgG	£1.20	

HBsAg		DAPS04, Clinical biochemistry, NHS reference costs 2019-20[33]
HCV Ab		
HIV Ab		
Hepatis A IgG		
Alpha-feto protein		

Abbreviations: Ab, antibody; ALP, alkaline Phosphatase; DNA, aeoxyribonucleic acid; GGT, gamma-glutamyl transferase; HBsAg, Hepatitis B surface antigen; HBV, hepatitis B virus; HCC; hepatocellular carcinoma; HCV, hepatitis C virus; HDV, hepatitis D virus; HIV, human immunodeficiency virus; INR, international normalized ratio; RNA, ribonucleic acid; TSH, thyroid stimulating hormone

*Cost updated in the company clarification response

Table 36. Monitoring costs per cycle applied in the model

	Bulevirtide patients		BSC patients/ bulevirtide patients off treatment	
	Non-cirrhotic	Compensated cirrhosis	Non-cirrhotic	Compensated cirrhosis
Treatment initiation	£365.45	£408.93	-	-
On treatment	£242.02	£289.26	£209.09*	£237.21
Off-treatment	£221.47	£237.21	£221.47	£237.21

Abbreviations: BSC, best supportive care.

*The cost presented here was used in the company's base case, but the EAG considers this is based on a calculation referencing error in the model. The EAG considers the correct cost should be £221.47, such that treatment status is not included for BSC patients.

4.2.8.10 Health state unit costs

As well as the inclusion of monitoring costs in the economic model, the company included health-state specific costs which were assumed to be independent of treatment and monitoring for CHD. To inform the health-state specific costs, the company performed a targeted literature review of UK specific costs relevant to CHD, but no relevant data were found. Instead, the company used health-state cost data relevant for the HBV and HCV population. Table 37 presents the health state costs applied in the model.

To inform the LT and PLT health state, data from Singh and Longworth, 2017[56] were used. Data from Singh and Longworth, 2017 were based on expert elicitation from clinical experts in liver transplantation as well as resource use obtained from NHS Blood and Transplant (NHSBT).[56]

For the remaining health states, costs were sourced from Shephard *et al.* 2006[57], which was also the source used to inform costs in NICE TA153.[53]

Additionally, as part of the F2 to F4 health state costs, the company assumed that 60% of patients are given an antiviral treatment (tenofovir 245 mg) for underlying HBV infection, based on the proportion of antiviral usage reported in MYR 301. The cost of tenofovir per model cycle was estimated to be £158.98 (see Table 64 of the CS for further details).

Table 37. Health state costs (Table 63 of the CS)

Health state	Unit cost	Source
F2	£887	CHB health state cost, Shephard *et al.* 2006,[57] inflated from 2007 values reported in NICE TA153[53] and weighted cost of tenofovir for underlying HBV infection.
F3	£887	
F4	£1,773	Compensated cirrhosis health state, Shephard *et al.* 2006,[57] inflated from 2007 values reported in NICE TA153[53] and weighted cost of tenofovir for underlying HBV infection.
Decompensated cirrhosis	£13,445	Shephard *et al.* 2006,[57] inflated from 2007 values reported in NICE TA153[53]
Hepatocellular carcinoma	£11,980	
Liver Transplant	£87,796	Singh and Longworth, 2017,[56] inflated from 2012/13 prices
Post-liver transplant	£25,949	

Abbreviations: CHB, chronic hepatitis B.

4.2.8.11 EAG critique

The EAG considers that there may be an overlap between monitoring costs and health state costs included in the model. The F2 and F3 health state costs were based on the CHB study from Shephard *et al*. 2006, which included the costs of monitoring patients while on treatment. During the clarification stage, the EAG requested, and the company provided a scenario where the health state costs for the F2 and F3 state are removed from the analysis, however this had limited impact on the ICER (see Table 41 in Section 5.1.2.3 for results).

It should be noted that the company's scenario also removed the costs for antiviral treatment for underlying HBV infection. Thus, the EAG conducted a scenario omitting F2 and F3 health state costs but kept the costs of antiviral treatment with tenofovir. Results of the EAG scenario are presented in Section 6.2.

For the compensated cirrhosis (F4); DC and HCC health states, costs from Shephard *et al*. were based on an observational study conducted during an HTA-funded trial for HCV. However, upon investigation of the primary source, the EAG could not verify what resource use was included in the cost associated with these health states. Given the company's estimation of specific HDV monitoring costs for patients in the F4 state, the EAG preference is also to remove the health state costs for the F4 state. Similar to the scenario removing the F2 and F3 health state costs, the company's scenario also removed the cost of antiviral treatment for underlying HBV infection and so the EAG has provided a corrected scenario in Section 6.2.

The EAG identified a couple of secondary issues with costs, related to the cost of liver biopsy and the choice of tenofovir solely for the treatment of underlying HBV infection (entecavir is also approved for treatment of HBV, but is more expensive), but these had minimal impact on the ICER.

4.2.8.12 Adverse event costs

The company included the cost of managing adverse events for bulevirtide and BSC in the first cycle of the model. The unit costs of AE management are summarised in Table 42 and were combined with the incidence rates observed in MYR 301 (outlined in Section 4.2.7). Unit costs were derived from NHS Reference Costs 2019-2020.[33] The total AE management cost for bulevirtide and BSC was £3.46 and £16.81, respectively.

Table 38. Adverse event unit costs (Table 65 of the CS)

Adverse event	Unit cost	Source
Neutropenia	£332	NHS reference costs 2019/20, weighted average of day-case Agranulocytosis (SA35A–E)[33]
Thrombocytopenia	£368	NHS reference costs 2019/20, weighted average of day-case thrombocytopenia SA12G- K[33]
Leukopenia	£457	NHS reference costs 2019/20, weighted average of day-case - Other haematological or Splenic disorders (SA08G-J)[33]

Abbreviations: CS, company submission.

5 Cost effectiveness results

5.1.1 Company's cost effectiveness results

Table 39 below presents the incremental cost-effectiveness results of the company's updated (i.e., post clarification) base case deterministic analysis. In the base case analysis, an incremental quality-adjusted life-year (QALY) gain of [redacted] over best supportive care (BSC) along with additional costs of [redacted] for the bulevirtide arm, generates an incremental cost-effectiveness ratio (ICER) of £40,562 per QALY. A proposed confidential patient access scheme (PAS) discount of [redacted] for bulevirtide is applied in the company's base case and is therefore reflected in the results presented in this report.

Table 39. Company's base case results

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	8.14	[redacted]	-	-	-	-
Bulevirtide	[redacted]	12.96	[redacted]	[redacted]	4.82	[redacted]	£40,562

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life years; QALY, quality adjusted life year

5.1.2 Company's sensitivity analyses

5.1.2.1 Probabilistic sensitivity analyses

The company performed probabilistic sensitivity analysis (PSA) to assess the joint parameter uncertainty around base case results. Incremental results from the company's PSA, arising from 1,500 simulations, are summarised in Table 40. A PSA scatterplot is presented in Figure 6 and a cost-effectiveness acceptability curve (CEAC) is presented in Figure 7. Based on these analyses, the probability that bulevirtide is cost effective versus best supportive care (BSC) is 0% at a willingness to pay (WTP) threshold of £20,000 and 0% at a WTP threshold of £30,000. The mean ICER from the company's PSA was £42,239.

The ERG considers the parameters and respective distributions chosen for PSA, outlined in Appendix M of the CS to be generally sound. The ERG also considers the probabilistic results to be comparable to the deterministic results.

Table 40. Company's probabilistic base case results

Interventions	Total Costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]	-	-	-
Bulevirtide	[redacted]	[redacted]	[redacted]	[redacted]	£42,239

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life years; QALY, quality adjusted life year

Figure 6. Probabilistic sensitivity analysis scatterplot (reproduced from Figure 18 of the company response to clarification questions appendix)

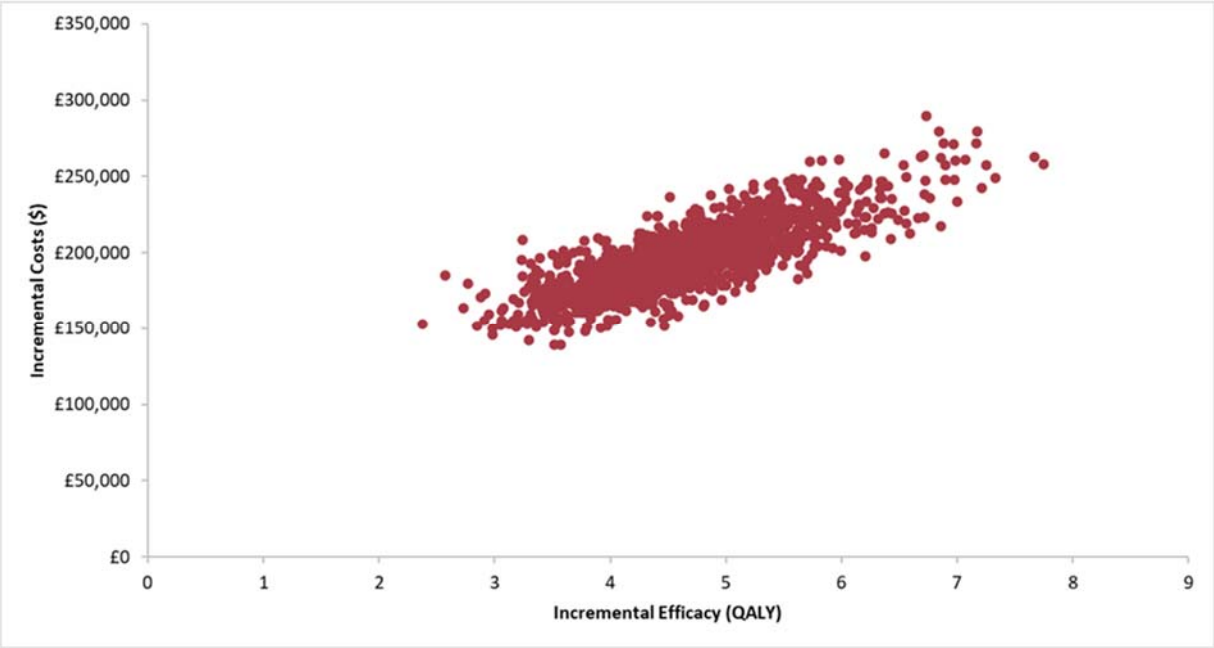
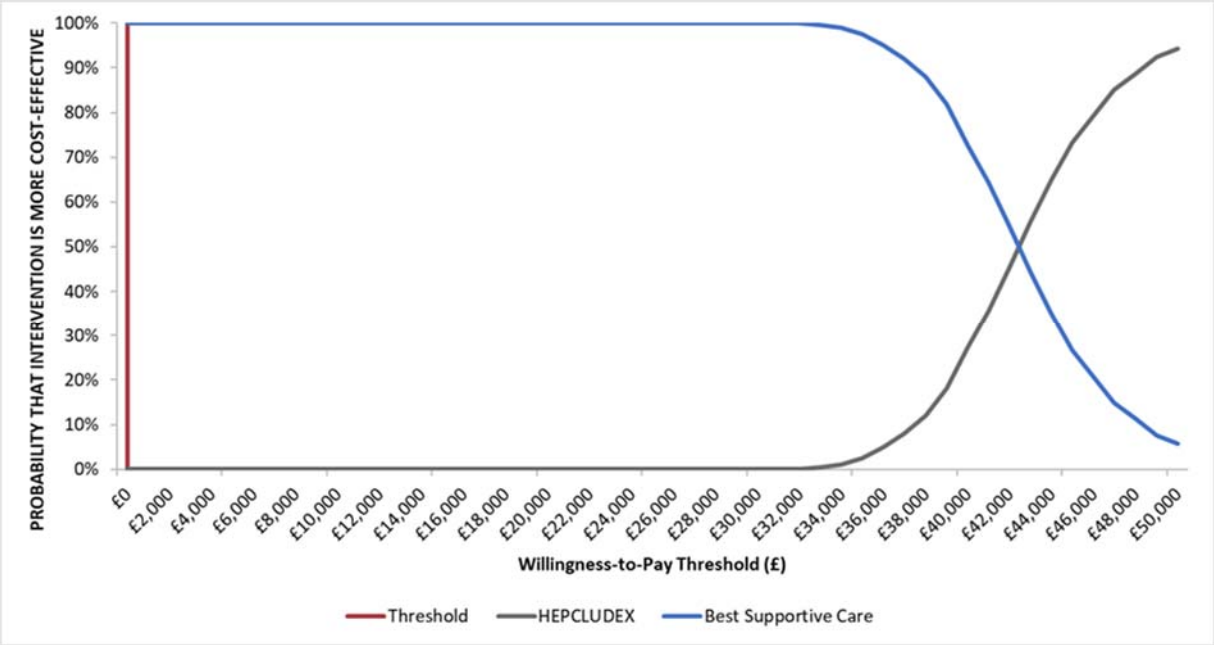


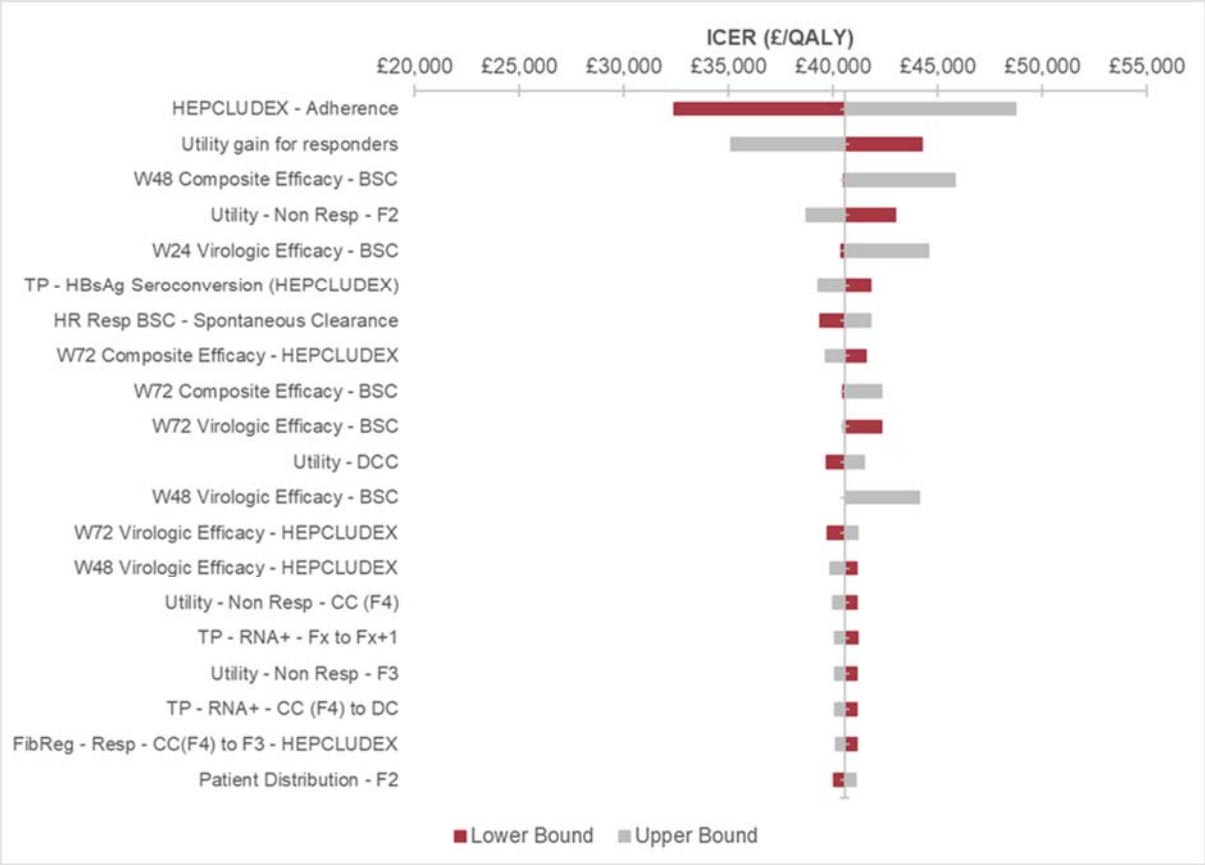
Figure 7. Cost-effectiveness acceptability curve - bulevirtide vs BSC (reproduced from Figure 19 of the company response to clarification questions appendix)



5.1.2.2 Deterministic sensitivity analyses

The company carried out one-way sensitivity analyses (OWSAs) to assess the impact of varying the key parameters between the upper and lower 95% confidence interval (CI) of the mean value. Where 95% CIs were not available, the company varied the mean value by +/-20%. The results of the OWSA are illustrated using the tornado diagram in Figure 8. The ICER was most sensitive to the adherence to bulevirtide treatment parameter, utility gain for responders and week 48 composite response for BSC.

Figure 8. Tornado plot - bulevirtide vs BSC (Figure 20 of the company response to clarification questions appendix)



5.1.2.3 Scenario analyses

The company undertook a series of scenario analyses to assess the impact of applying alternative assumptions to key model parameters. These scenarios are presented in Table 41. Additionally, the company conducted several scenario analyses requested by the EAG, also presented in Table 41.

Table 41. Company scenario analyses

Base case assumption	Alternative scenario	ICER (£/QALY)
Company updated base case	**-**	**£40,562**
Patients baseline fibrosis status - F2-F4	Patients baseline fibrosis status - F3-F4	£38,317
Inclusion of utility gain for responder	Exclusion of utility gain for responders	£44,259
Inclusion of fibrosis regression	Exclusion of fibrosis regression	£46,253
HR for progression of 0 in complete responders	HR for progression is half that of the partial responders	£43,446
Definition of responder - composite	Definition of responder - virologic	£48,270

Extrapolation of Week 48 MYR 301 response data - Yes	Extrapolation of Week 48 MYR 301 response data - No	£41,468
Source of non-responder health state utility values for mild-moderate health states - CHB meta-analysis for F0-F4	Source of non-responder health state utility values for mild-moderate health states - MYR 301 for F0-F4	£41,808
Source of health state utility values for all non-responder health states - CHB meta-analysis	Source of health state utility values for all non-responder health states - HCV meta-analysis	£41,970
AE utility decrements included	AE utility decrements excluded	£40,562
Cost of antiviral medication included	Cost of antiviral medication excluded	£40,450
Cost of fibroscan and liver biopsy included	Cost of fibroscan and liver biopsy excluded	£40,482
EAG requested scenarios		
Patients baseline fibrosis status - F2-F4	Health states F2 and F3 are aggregated and removal of disease regression below F3	£38,535
Lower probability of HCC for responders	Impact of response on probability of HCC removed	£51,565
Constant annual probability of death for HCC patients and constant annual probability of DCC	Survival analysis of data from Bolondi *et al.*, 2001 (HCC mortality) and Fattovich *et al.*, 2003[42] (DCC)	£43,493
Fibrosis regression starts occurring within the first 24 weeks of treatment (i.e., first model cycle).	Fibrosis regression only starts occurring from cycle 4 onwards (i.e., 96 weeks) in the model	£40,901
No age-related disutility adjustments	Age-related disutility adjustments included	£43,898
F2 and F3 health state cost included	F2 and F3 health state cost excluded	£39,658
F4 health state cost included	F4 health state cost excluded	£39,388
Cost of fibroscan and liver biopsy - £43.93 (cost code RD48Z, lower costs)[33]	Cost of fibroscan and liver biopsy - £129.17 (cost code RD48Z, higher cost)[33]	£40,723
	Cost of liver biopsy - £129.17 (cost code RD48Z, higher cost)[33]	£40,605
Abbreviations: CHB, chronic hepatitis B; HCV, hepatitis C virus; HR, hazard ratio		

5.1.3 Model validation and face validity check

The company stated that the model was developed internally by a team of health economists, with the structure and clinical assumptions validated by an advisory board which included UK clinical and health economic experts.

The EAG identified and corrected two minor errors in the model regarding the calculation of the baseline distribution of patients amongst fibrosis stages and monitoring costs for BSC. Please refer to Section 6.1 for details of the EAG corrections.

6 Additional economic analysis undertaken by the EAG

6.1 Model corrections

The EAG identified and corrected two minor errors in the model regarding the calculation of the baseline distribution of patients amongst fibrosis stages and monitoring costs for BSC.

As described in Section 4.2.2, the company used an incorrect estimate from Spaan *et al*. 2020[35] to inform the baseline cirrhosis estimate in the model. The EAG corrected the proportion of patients cirrhotic at baseline to 50% in the company's estimations and the reweighted baseline distribution of patients amongst the fibrosis stages is presented in Table 42.

Table 42. EAG corrected baseline distribution of patients amongst fibrosis stages (Table 36 and Table 37 of the CS)

Health states	Proportion of patients - base case	Proportion of patients - scenario	Source
F2 (non-cirrhotic)	14.9%	-	Spaan *et al.* 2020[35], reweighted using Romeo *et al.* 2009[2]
F3 (non-cirrhotic)	21.2%	24.9%	
F4 (compensated cirrhosis)	63.9%	75.1%	

Abbreviations: CS, company submission.

With regards to the monitoring cost for BSC, the EAG found a calculation referencing error in the model for the monitoring cost of BSC patients who are non-cirrhotic (see Table 36, Section 4.2.8.9), which resulted in a differential cost based on treatment status (which is not relevant for this arm of the model). The corrected cost of monitoring for non-cirrhotic BSC patients should be £221.47. Table 43 presents the corrected company base case results.

Table 43. Corrected company's base case results

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	7.95	[redacted]	-	-	-	-
Bulevirtide	[redacted]	12.78	[redacted]	[redacted]	4.83	[redacted]	£40,189

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life years; QALY, quality adjusted life year

6.2 EAG scenario analysis

The scenario analyses undertaken by the EAG are explained throughout the report. Results of the exploratory analyses conducted using the trial population are reported in Table 44. The following analyses were conducted:

1. The EAG changed the mean age and cirrhotic distribution at baseline to reflect the MYR 301 population (42 years and 47% of patients with compensated cirrhosis) – Section 4.2.2.
2. The EAG has conducted a scenario analysis where 48 weeks is the maximum timeframe for assessing final response to treatment, and where treatment effectiveness is not extrapolated – Section 4.2.4.
3. The EAG used the observed trial data to estimate TPs in the economic model for bulevirtide and BSC – Section 4.2.5.2.
4. Estimation of the probability of HCC from the F2-F4 states according to Fattovich[8] and Kushner[3] - Table 25, Section 4.2.5.3.1.
5. Estimation of the probability of HCC from the F2-F4 states according to Romeo[2] and Kushner[3] - Table 25, Section 4.2.5.3.1.
6. Estimation of the probability of fibrosis progression from the F2-F4 states according to Romeo[2]- Section 4.2.5.3.1.
7. Assuming that CRs have the same probability as PRs (which is lower than the probability of NRs) of developing HCC, instead of having a 0% probability of HCC.
8. Using the 0.81 utility value to estimate the quality of life for NRs and PRs in the F-states, together with assuming a [redacted] utility value for CRs; and assuming that PLT patients experience a [redacted] utility after transplant – Section 4.2.8.
9. Using the 0.81 utility value to estimate the quality of life for NRs and PRs in the F-states, together with assuming a [redacted] utility value for CRs; and applying the relative difference from TA173 between the CC state and the DC, HCC, LT, and PLT – Section 4.2.8.
10. Removing the utility gain associated with being a CR – Section 4.2.8.
11. Adjusting utilities as per Ara and Brazier[1] – Section 4.2.8.
12. Assuming that responders in the HCC health state carry on with bulevirtide treatment – Section 4.2.10.
13. Removing the F2 and F3 health state costs and including antiviral treatment costs for underlying HBV infection - Section 4.2.10.

14. Removing the F4 health state costs and including antiviral treatment costs for underlying HBV infection - Section 4.2.10.

The results in Table 44 show that none of the scenarios ran in isolation have a considerable impact on the final ICER, with increases not exceeding £4,000 per QALYs gained. The model key drivers are the assumption that CRs have a utility gain (in all F-states) compared to PRs and NRs, replacing the baseline characteristics in the model by those observed in the MYR 301 trial and adjusting the utilities for patients' age as per Ara and Brazier[1].

Table 44. Results of the EAG's scenario analyses

	Results per patient	Intervention	Comparator	Incremental value
0	**Corrected company base case**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£40,189
1	The EAG changed the mean age and cirrhotic distribution at baseline to reflect the MYR 301 population (42 years and 47% of patients with compensated cirrhosis) – Section 4.2.2.			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£43,594
2	The EAG has conducted a scenario analysis where 48 weeks is the maximum timeframe for assessing final response to treatment, and where treatment effectiveness is not extrapolated – Section 4.2.4.			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£40,851
3	The EAG used the observed trial data to estimate TPs in the economic model for bulevirtide and BSC – Section 4.2.5.2.			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£39,519
4	Estimation of the probability of HCC from the F2-F4 states according to Fattovich[8] and Kushner[3] - Table 20, Section 4.2.5.3.1			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£41,864
5	Estimation of the probability of HCC from the F2-F4 states according to Romeo[2] and Kushner[3] - Table 20, Section 4.2.5.3.1			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£40,828

6	Estimation of the probability of fibrosis progression from the F2-F4 states according to Romeo-- Table 21, Section 4.2.5.3.1			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£41,308
7	Assuming that CRs have the same probability as PRs (which is lower than the probability of NRs) of developing HCC, instead of having a 0% probability of HCC.			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£42,909
8	Using the 0.81 utility value to estimate the quality of life for NRs and PRs in the F-states, together with assuming a [redacted] utility value for CRs; and assuming that PLT patients experience a [redacted] utility after transplant – Section 4.2.8.			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£41,488
9	Using the 0.81 utility value to estimate the quality of life for NRs and PRs in the F-states, together with assuming a [redacted] utility value for CRs; and applying the relative difference from TA173 between the CC state and the DC, HCC, LT, and PLT – Section 4.2.8.			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£41,012
10	Removing the utility gain associated with being a CR – Section 4.2.8.			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£43,821
11	Adjusting utilities as per Ara and Brazier – Section 4.2.8.			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£43,474
12	Inclusion of treatment costs for responders in the DC and HCC health states - Section 4.2.10			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£40,199
13	Removal of F2 and F3 health state costs + costs of antiviral treatment - Section 4.2.10			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£39,397
14	F4 health state costs + costs of antiviral treatment - Section 4.2.10			
	Total costs (£)	[redacted]	[redacted]	[redacted]

	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£39,105

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

6.3 EAG preferred assumptions

The EAG's preferred assumptions (as labelled in the previous section) are the following:

2. Assuming that 48 weeks is the maximum timeframe for assessing final response to treatment, and treatment effectiveness is not extrapolated – Section 4.2.4.
3. Using the observed trial data to estimate TPs in the economic model for bulevirtide and BSC – Section 4.2.5.2.
5. Estimation of the probability of HCC from the F2-F4 states according to Romeo[2] and Kushner[3] - Table 25, Section 4.2.5.3.1.
6. Estimation of the probability of fibrosis progression from the F2-F4 states according to Romeo[2]- Table 26, Section 4.2.5.3.1.
7. Assuming that CRs have the same probability as PRs (which is lower than the probability of NRs) of developing HCC, instead of having a 0% probability of HCC.
8. Using the 0.81 utility value to estimate the quality of life for NRs and PRs in the F-states, together with assuming a [redacted] utility value for CRs; and assuming that PLT patients experience a [redacted] utility after transplant – Section 4.2.8.
11. Adjusting utilities as per Ara and Brazier – Section 4.2.8.
12. Assuming that responders in the DC and HCC health states carry on with bulevirtide treatment – Section 4.2.10.
13. Removing the F2 and F3 health state costs and including antiviral treatment costs for underlying HBV infection - Section 4.2.10.
14. Removing the F4 health state costs and including antiviral treatment costs for underlying HBV infection - Section 4.2.10.

In addition to these assumptions, the EAG also produced an ICER with cumulative changes including the mean age and cirrhotic distribution at baseline to reflect the MYR 301 population (42 years and 47% of patients with compensated cirrhosis).

The cumulative EAG-preferred assumptions (Table 45), when external literature is used to estimate baseline characteristics, result in a final ICER of £48,518 per QALY gained; when MYR 301 is used to estimate baseline characteristics the ICER increases to £57,541.

While the EAG's clinical experts considered that the baseline characteristics included in the company's model were representative of the UK population, they noted that the baseline characteristics in the trial were not clinically implausible. Given the considerable impact that this assumption has on the final ICER, the EAG recommends that the committee seeks clinical expert opinion to assess the plausibility of the population characteristics in both scenarios. It is the EAG's opinion that the "true" ICER probably lies in between the two values.

Finally, the EAG notes that removing the utility gain associated with being a CR increases the EAG's ICER to £53,744 when external literature is used to estimate baseline characteristics, and to £64,765 when MYR 301 is used to estimate baseline characteristics.

Table 45. EAG's preferred model assumptions

Preferred assumption	Section in EAG report	Cumulative ICER (£/QALY)
Company base case (corrected)	Section 6.1	£40,189
Assuming that 48 weeks is the maximum timeframe for assessing final response to treatment, and treatment effectiveness is not extrapolated	Section 4.2.4.	£40,851
Using the observed trial data to estimate TPs in the economic model for bulevirtide and BSC	Section 4.2.5.2.	£39,734
Estimation of the probability of HCC from the F2-F4 states according to Romeo[2] and Kushner[3]	Table 20, Section 4.2.5.3.1	£40,363
Estimation of the probability of fibrosis progression from the F2-F4 states according to Romeo	Table 21, Section 4.2.5.3.1	£42,173
Assuming that CRs have the same probability as PRs (which is lower than the probability of NRs) of developing HCC, instead of having a 0% probability of HCC.	Section 4.2.5.3.1	£44,058
Using the 0.81 utility value to estimate the quality of life for NRs and PRs in the F-states, together with assuming a [redacted] utility value for CRs; and assuming that PLT patients experience a [redacted] utility after transplant	Section 4.2.8.	£45,512
Adjusting utilities as per Ara and Brazier	Section 4.2.8.	£49,387

Assuming that responders in the HCC health states carry on with bulevirtide treatment	Section 4.2.10.	£49,744
Removing the F2 and F3 health state costs and including antiviral treatment costs for underlying HBV infection	Section 4.2.10.	£48,853
Removing the F4 health state costs and including antiviral treatment costs for underlying HBV infection	Section 4.2.10.	£48,518
The EAG changed the mean age and cirrhotic distribution at baseline to reflect the MYR 301 population (42 years and 47% of patients with compensated cirrhosis)	Section 4.2.2.	£57,541

Abbreviations: EAG, evidence review group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

6.4 Conclusions of the cost effectiveness sections

Overall, the EAG considers that the key uncertainties around the company's estimation of cost effectiveness are the baseline age and cirrhotic distribution of patients. The company assumed that 60% of patients at baseline had CC, while the equivalent proportion in the MYR 301 trial was 47%. The company also assumed that patients were 35 years old at baseline, while this was 42 years in the trial. These assumptions have a considerable impact on the final ICER and thus the EAG recommends that: 1) the company presents available data from literature during technical engagement to ascertain the typically presenting age and cirrhotic distribution of CHD patients in the UK; 2) the committee seeks clinical expert opinion to validate these assumptions.

The EAG is also concerned that CR rates were greater in the non-cirrhotic subgroup, hence the overall estimate of CR from MYR 301 may overestimate the clinical efficacy of bulevirtide for patients with METAVIR staging F2 and above. Therefore, the EAG requested that the company undertook a subgroup analysis by cirrhosis presence at baseline to be the best proxy for estimating the contribution of participants with METAVIR stages F0 and F1 to the overall trial results. The company did not undertake the analysis and therefore the EAG asks that the company reconsiders this at technical engagement.

7 Severity modifier

As outlined in the NICE methods guide,[51] "*the committee will consider the severity of the condition, defined as the future health lost by people living with the condition with standard care in the NHS*". The thresholds of QALY weightings for severity are reported in Table 49.

Table 46. QALY weighting for severity

QALY weight	Proportional QALY shortfall	Absolute QALY shortfall
1	Less than 0.85	Less than 12
x1.2	0.85 to 0.95	12 to 18
x1.7	At least 0.95	At least 18.

Abbreviations: QALY, quality-adjusted life-year

The company calculated the absolute and proportional QALY shortfall using a published calculator by Schneider *et al*. 2021.[58] The tool calculates the expected total QALYs for the general population matched to baseline age and sex distribution included in the economic model. The source of the general population EQ-5D data used in the calculator is from a study by Hernandez *et al*. 2020.[59] Table 47 presents the company's preferred assumptions for the general population QALY shortfall estimates.

Table 47. Summary of preferred assumptions for general population QALY shortfall estimates

Factor	Value or source (reference to appropriate table or figure in submission)	Reference to section in submission or rationale
Sex distribution - % male	58.7%	Section 4.2.2
Starting age	35.1 years	Section 4.2.2
Expected total QALYs for the general population	18.94	Schneider *et al*. 2021.[58]. Estimate based on starting age and sex distribution at baseline
Discount rate	3.5%	Section 4.2.4

Abbreviations: QALY, quality-adjusted life-year

To calculate the absolute and proportional QALY shortfall using the calculator, the company used the base case total QALYs estimated for the BSC arm, estimated to be [redacted]. The results of the company's QALY shortfall analysis is presented in Table 48 and Table 49 presents a summary of health state benefits and utility values for the QALY shortfall analysis. Table 50 presents a summary of the company's preferred assumptions for the BSC QALY shortfall estimates.

Table 48. Company's QALY shortfall analysis

Category	Estimated QALYs
Without the disease - age and sex matched general population	18.94
With the disease - patients on BSC	[redacted]
Absolute shortfall	[redacted]
Proportional shortfall	[redacted]

Abbreviations: BSC, best supportive care; QALY, quality adjusted life year

Table 49. Summary of QALY gain in the model

State	Discounted QALY gain
F2	0.98
F3	1.63
F4 (compensated cirrhosis)	2.66
DCC	0.48
HCC	0.22
LT	0.01
PLT	0.14
AEs	-0.004

Table 50. Summary of preferred assumptions for standard care QALY shortfall estimates

Modelled input	Assumption or value (reference to appropriate table or figure in submission)	Company's rationale or justification
Treatment effectiveness		
Natural history of disease - transition probabilities for non-responders	Described in Section 4.2.5.3	Described in Section 4.2.5.3. Based on the company's assumption that HBV estimates should be used and adjusted with HBV/HDV coinfection multipliers
Health state utility values		
F2/F3	NR/PR = 0.85 CR = [redacted]	Section 4.2.8. Based on the meta-analysis of CHB utility values and includes a utility gain for responders
F4 (compensated cirrhosis)	NR/PR = 0.76 CR = [redacted]	Section 4.2.8. Based on the meta-analysis of CHB utility values and includes a utility gain for responders
DCC	0.46	Section 4.2.8. Based on the meta-analysis of CHB utility values
HCC	0.52	Section 4.2.8. Based on the meta-analysis of CHB utility values
LT	0.57	Section 4.2.8. Based on the meta-analysis of CHB utility values

PLT	0.67	Section 4.2.8. Based on the meta-analysis of CHB utility values
Age-related disutility	Not included	Section 4.2.8.5. Company did not justify why utilities were not adjusted for age. However, the company did provide a scenario where utilities were adjusted for age.

Abbreviations: AE, adverse events; CHB, chronic hepatitis B; CR, complete responder; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LT, liver transplant; NR, non-responder; PLT, post liver transplant; PR, partial responder;

Based on the QALY shortfall analysis, the company estimated that a severity modifier of 1.2 should be considered by the committee. Table 51 presents the company's preferred cost-effectiveness results without the severity weighting and Table 52 presents the same results with the severity modifier of 1.2 applied to the incremental QALYs.

Table 51. Cost effectiveness results without severity weighting

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALYs)
Company base case	[redacted]	[redacted]	£40,562

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Table 52. Cost effectiveness results with 1.2 severity weighting

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALYs)
Company base case	[redacted]	[redacted]	£33,802

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

7.1.1 EAG critique

The EAG considers the Schneider *et al*. calculator an appropriate tool to estimate absolute and proportional QALYs. None of the EAG's preferred assumptions alter the QALY shortfall weight of 1.2 estimated by the company, with the exception of baseline age. When the baseline age (42 years) from the MYR 301 trial is used in the shortfall estimation, the weight decreases to 1 (Table 53). Therefore, as discussed in Section 6.3, the EAG recommends that the committee seeks clinical expert opinion to assess the clinical plausibility of the population characteristics in both scenarios, and whether a baseline age of 35 or 42 years is more representative of patients with CHD in the UK.

The results of the EAG's QALY shortfall analysis are presented in Table 54 and Table 55 when external literature is used to estimate baseline characteristics, without and with the severity weighting, respectively. Table 56 reports the ICER when MYR 301 is used to estimate baseline characteristics. Given the severity weighting is 1 in this scenario, the results with or without the weighting are the same.

Table 53. EAG's QALY shortfall factors

Factor	Company's base case	EAG's ICER using external literature to estimate baseline characteristics	EAG's ICER using MYR 301 baseline characteristics
Sex distribution - % male	58.7%	58.7%	58.7%
Starting age	35.1 years	35.1 years	42 years
Expected total QALYs for the general population	18.94	18.94	17.33
Discount rate	3.5%	3.5%	3.5%
Total QALYs estimated for BSC	[redacted]	[redacted]	[redacted]*
Severity weighting	1.2	1.2	1

Abbreviations: QALY, quality-adjusted life-year

*The total QALYs estimated for BSC increase in the EAG's ICER using MYR 301 baseline characteristics in comparison to the EAG's ICER using external literature because of the baseline distribution of cirrhotic patients. If only age was changed the total BSC QALYs would decrease to [redacted]. This would not change the severity weighting, which would still be 1 in this scenario.

Table 54. EAG's ICER using external literature to estimate baseline characteristics without severity weighting

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALYs)
EAG's ICER using external literature	[redacted]	[redacted]	£48,518

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Table 55. EAG's ICER using external literature to estimate baseline characteristics with 1.2 severity weighting

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALYs)
EAG's ICER using external literature	[redacted]	[redacted]	£40,431

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Table 56. EAG's ICER using MYR 301 baseline characteristics with and without severity weighting

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALYs)
EAG's ICER using MYR 301	[redacted]	[redacted]	£57,541

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Table 57. Summary of QALY gain in the model using external literature to estimate baseline characteristics

State	Discounted QALY gain
F2	1.33
F3	2.15

F4 (compensated cirrhosis)	2.33
DCC	0.56
HCC	0.18
LT	0.01
PLT	0.18
AEs	-0.004

Table 58. Summary of QALY gain in the model using MYR 301 baseline characteristics

State	Discounted QALY gain
F2	1.83
F3	3.02
F4 (compensated cirrhosis)	1.99
DCC	0.48
HCC	0.17
LT	0.01
PLT	0.15
AEs	-0.004

8 References

1. Ara R, Brazier J. Deriving an algorithm to convert the eight mean SF-36 dimension scores into a mean EQ-5D preference-based score from published studies (where patient level data are not available). *Value Health* 2008; **11**: 1131-43.
2. Romeo R, Del Ninno E, Rumi M, Russo A, Sangiovanni A, de Franchis R, et al. A 28-Year Study of the Course of Hepatitis Δ Infection: A Risk Factor for Cirrhosis and Hepatocellular Carcinoma. *Gastroenterology* 2009; **136**: 1629-38.
3. Tatyana Kushner MS, David Kaplan. Delta Hepatitis within the Veterans Affairs Medical System in the United States: Prevalence, Risk Factors, and Outcomes. *Journal of Hepatology* 2015; **63**: 586-92.
4. Miao Z, Zhang S, Ou X, Li S, Ma Z, Wang W, et al. Estimating the global prevalence, disease progression, and clinical outcome of hepatitis delta virus infection. *Journal of Infectious Diseases* 2020; **221**: 1677-87.
5. Yurdaydin C, Idilman R, Bozkaya H, Bozdayi AM. Natural history and treatment of chronic delta hepatitis. *Journal of viral hepatitis* 2010; **17**: 749-56.
6. Negro F. Hepatitis D virus coinfection and superinfection. *Cold Spring Harbor Perspectives in Medicine* 2014; **4**.
7. Béguelin C, Moradpour D, Sahli R, Suter-Riniker F, Lüthi A, Cavassini M, et al. Hepatitis delta-associated mortality in HIV/HBV-coinfected patients. *Journal of hepatology* 2017; **66**: 297-303.
8. Fattovich G, Giustina G, Christensen E, Pantalena M, Zagni I, Realdi G, et al. Influence of hepatitis delta virus infection on morbidity and mortality in compensated cirrhosis type B. *Gut* 2000; **46**: 420-6.
9. Heidrich B, Yurdaydin C, Kabaçam G, Ratsch BA, Zachou K, Bremer B, et al. Late HDV RNA relapse after peginterferon alpha-based therapy of chronic hepatitis delta. *Hepatology* 2014; **60**: 87-97.
10. Axley P, Mudumbi S, Sarker S, Kuo YF, Singal A. Patients with stage 3 compared to stage 4 liver fibrosis have lower frequency of and longer time to liver disease complications. *PLoS ONE* 2018; **13**.
11. Bockmann JH, Grube M, Hamed V, Von Felden J, Landahl J, Wehmeyer M, et al. High rates of cirrhosis and severe clinical events in patients with HBV/HDV co-infection: longitudinal analysis of a German cohort. *BMC Gastroenterol* 2020; **20**.
12. Golabi P, Fazel S, Otgonsuren M, Sayiner M, Locklear CT, Younossi ZM. Mortality assessment of patients with hepatocellular carcinoma according to underlying disease and treatment modalities. *Medicine (United States)* 2017; **96**.
13. Grabowski J, Wedemeyer H. Hepatitis delta: Immunopathogenesis and clinical challenges. Karger Publishers; 2010. p. 133-8.
14. European Medicines Agency. Hepcludex, 2021. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/hepcludex. Date accessed: 23 Jun 2022.
15. G.S.I. Data on file. Advisory Board Report. 2022.
16. European Medicines Agency. Hepcludex: Orphan Maintenance Assessment Report, 2020. Available from: https://www.ema.europa.eu/en/documents/orphan-maintenance-report/hepcludex-orphan-maintenance-assessment-report_en.pdf. Date accessed: 23 Jun 2022.
17. National Institute for Health and Care Excellence (NICE). Hepatitis B (chronic): diagnosis and management | Guidance | NICE, 2017. Available from: https://www.nice.org.uk/guidance/cg165/ifp/chapter/drug-treatment. Date accessed: 23 Jun 2022.
18. European Medicines Agency. Pegasys - Summary of Product Characteristics (SmPC), 2022. Available from: https://www.ema.europa.eu/en/documents/product-information/pegasys-epar-product-information_en.pdf. Date accessed: 23 Jun 2022.
19. National Institute for H, Care E, inventorsAdefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B2006.

20. Farci P, Niro GA. Current and future management of chronic hepatitis D. *Gastroenterology and Hepatology* 2018; **14**: 342-51.
21. Rizzetto M, Hamid S, Negro F. The changing context of hepatitis D. *Journal of hepatology* 2021; **74**: 1200-11.
22. Sleijfer S, Bannink M, Van Gool AR, Kruit WHJ, Stoter G. Side effects of interferon-alpha therapy. *Pharmacy world & science : PWS* 2005; **27**: 423-31.
23. Lampertico P, Agarwal K, Berg T, Buti M, Janssen HLA, Papatheodoridis G, et al. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *Journal of Hepatology* 2017; **67**: 370-98.
24. National Institute for Health and Care Excellence (NICE). Final scope for the appraisal of bulevirtide for treating chronic hepatitis D [ID3732]. 2022. Available from: https://www.nice.org.uk/guidance/gid-ta10652/documents/final-scope. Date accessed: 23 Jun 2022.
25. Medicines Healthcare Products Regulatory Agency (MHRA). Hepcludex - Summary of Product Characteristics (SmPC), 2021. Available from: https://mhraproducts4853.blob.core.windows.net/docs/0e955410fdcb17b4ac09e9357f24a2034234da06. Date accessed: 23 Jun 2022.
26. Wedemeyer H, Aleman S, Andreone P, Blank A, Brunetto M, Bogomolov P, et al. Bulevirtide Monotherapy at Low and High Doses in Patients With Chronic Hepatitis Delta: 24-Week Interim Data of the Phase 3 MYR301 Study. *Journal of hepatology* 2021; **75**: S294-803.
27. Wedemeyer H, Schöneweis K, Bogomolov PO, Voronkova N, Chulanov V, Stepanova T, et al. Final results of a multicenter, open-label phase 2 clinical trial (MYR203) to assess safety and efficacy of myrcludex B in with PEG-interferon Alpha 2a in patients with chronic HBV/HDV co-infection. Elsevier BV, 2019.
28. Centre for R, Dissemination. Systematic Reviews: CRD"s guidance for undertaking reviews in health care. 2009 978-1-900991-19-3.
29. file GSIDo. MYR 202 Clinical Study Report. 2019.
30. Carobene A, Braga F, Roraas T, Sandberg S, Bartlett WA. A systematic review of data on biological variation for alanine aminotransferase, aspartate aminotransferase and gamma-glutamyl transferase. *Clin Chem Lab Med* 2013; **51**: 1997-2007.
31. Schmidt MI, Bracco P, Canhada S, Guimaraes JMN, Barreto SM, Chor D, et al. Regression to the Mean Contributes to the Apparent Improvement in Glycemia 3.8 Years After Screening: The ELSA-Brasil Study. *Diabetes Care* 2021; **44**: 81-8.
32. Ruggieri A, Gagliardi MC, Anticoli S. Sex-Dependent Outcome of Hepatitis B and C Viruses Infections: Synergy of Sex Hormones and Immune Responses? *Front Immunol* 2018; **9**: 2302.
33. NHS. National schedule of NHS costs 2019-20. 2021.
34. BNF. British National Formulary. 2021. Available from: https://bnf.nice.org.uk/. Date accessed.
35. Spaan M, Carey I, Bruce M, Shang D, Horner M, Dusheiko G, et al. Hepatitis delta genotype 5 is associated with favourable disease outcome and better response to treatment compared to genotype 1. *Journal of Hepatology* 2020; **72**: 1097-104.
36. Farci P, Roskams T, Chessa L, Peddis G, Mazzoleni AP, Scioscia R, et al. Long-term benefit of interferon α therapy of chronic hepatitis D: regression of advanced hepatic fibrosis. *Gastroenterology* 2004; **126**: 1740-9.
37. Marcellin P, Gane E, Buti M, Afdhal N, Sievert W, Jacobson IM, et al. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study. *Lancet (London, England)* 2013; **381**: 468-75.
38. 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. *Journal of Hepatology* 2020; **73**: 533-9.

39. Hsu YS, Chien RN, Yeh CT, Sheen IS, Chiou HY, Chu CM, et al. Long-term outcome after spontaneous HBeAg seroconversion in patients with chronic hepatitis B. *Hepatology* 2002; **35**: 1522-7.
40. Dienstag JL, Ghany MG, Morgan TR, Di Bisceglie AM, Bonkovsky HL, Kim HY, et al. A prospective study of the rate of progression in compensated, histologically advanced chronic hepatitis C. *Hepatology* 2011; **54**: 396-405.
41. Bermingham SL, Hughes R, Fenu E, Sawyer LM, Boxall E, T.Kennedy P, et al. Cost-Effectiveness Analysis of Alternative Antiviral Strategies for the Treatment of HBeAg-Positive and HBeAg-Negative Chronic Hepatitis B in the United Kingdom. *Value in Health* 2015; **18**: 800-9.
42. Fattovich G. Natural history and prognosis of hepatitis B. Copyright © 2002 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA. Tel.: +1(212) 584-4662; 2003. p. 47-58.
43. Da BL, Heller T, Koh C. Hepatitis D infection: From initial discovery to current investigational therapies. *Gastroenterology Report* 2019; **7**: 231-45.
44. Dakin H, Bentley A, Dusheiko G. Cost-utility analysis of tenofovir disoproxil fumarate in the treatment of chronic hepatitis B. *Value in Health* 2010; **13**: 922-33.
45. Kamal H, Westman G, Falconer K, Duberg AS, Weiland O, Haverinen S, et al. Long-Term Study of Hepatitis Delta Virus Infection at Secondary Care Centers: The Impact of Viremia on Liver-Related Outcomes. *Hepatology* 2020; **72**: 1177-90.
46. Roulot D, Brichler S, Layese R, BenAbdesselam Z, Zoulim F, Thibault V, et al. Origin, HDV genotype and persistent viremia determine outcome and treatment response in patients with chronic hepatitis delta. *Journal of Hepatology* 2020; **73**: 1046-62.
47. file GSIDo. HDV utility analysis. 2022.
48. Gilead - Data on f. Meta-analyses of Health State Utilities in cHCV and cHBV. 2022.
49. Tolley K, Goad C, Yi Y, Maroudas P, Haiderali A, Thompson G. Utility elicitation study in the UK general public for late-stage chronic lymphocytic leukaemia. *The European journal of health economics : HEPAC : health economics in prevention and care* 2013; **14**: 749-59.
50. Sullivan PW, Slejko JF, Sculpher MJ, Ghushchyan V. Catalogue of EQ-5D Scores for the United Kingdom. *Medical Decision Making* 2011; **31**: 800-4.
51. NICE. NICE health technology evaluations: the manual. 2022.
52. NICE. Tenofovir disoproxil for the treatment of chronic hepatitis B (TA173). 2009.
53. NICE. Entecavir for the treatment of chronic hepatitis B (TA153). 2008.
54. Levy AR, Kowdley KV, Iloeje U, Tafesse E, Mukherjee J, Gish R, et al. The impact of chronic hepatitis B on quality of life: A multinational study of utilities from infected and uninfected persons. *Value in Health* 2008; **11**: 527-38.
55. Ossa DF, Briggs AH, Tafesse E, Iloeje U, Mukherjee J, Lozano-Ortega G, et al. Impact on Quality of Life of Health States Induced By Chronic Hepatitis B Infection: Estimates From Uninfected and Infected Persons in the UK. *Value in Health* 2005; **8**: A60-A.
56. Singh J, Longworth L. Comparison of methods for estimating contemporary costs: an application to liver transplantation in the United Kingdom. *International Journal of Technology Assessment in Health Care* 2017; **33**: 620-8.
57. Shepherd JJJ, Baxter L, Gospodarevskaa E, Hartwell D, Harris P, Price A. Adefovir dipivoxil and pegylated interferon alpha for the treatment of chronic hepatitis B: An updated systematic review and economic evaluation. *Health Technology Assessment* 2006; **13**.
58. Schneider P, McNamara S, Love-Koh J, Doran T, Gutacker N. Quality-adjusted life expectancy norms for the English population. 2021.
59. Hernandez Alava M, Pudney S, Wailoo A. Estimating the relationship between EQ-5D-5L and EQ-5D-3L: results from an English Population Study. 2020.

60. Centre for Reviews and Dissemination (CRD). CRD's guidance for undertaking reviews in healthcare. *Available at https://wwwyorkacuk/media/crd/Systematic_Reviewspdf (Accessed 21 March 2016)* 2011.
61. Veenstra DL, Sullivan SD, Dusheiko GM, Jacobs M, Aledort JE, Lewis G, et al. Cost-effectiveness of peginterferon α-2a compared with lamivudine treatment in patients with HBe-antigen-positive chronic hepatitis B in the United Kingdom. *European Journal of Gastroenterology and Hepatology* 2007; **19**: 631-8.

9 Appendices

9.1 Safety data MYR 301

Table 59. Summary of adverse events, MYR 301 (safety analysis set, table reproduced from Table 28, CS)

	Delayed Treatment (n=51)	BLV 2mg (n=49)	BLV 10mg (n=50)	Total (n=150)
Total number of AEs, n	[redacted]	[redacted]	[redacted]	[redacted]
Any AE, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAE, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Any serious TEAE, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAE leading to the withdrawal of the study medication, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAE leading to death, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
TEAE by severity, n (%)				
Grade 1 (mild)	[redacted]	[redacted]	[redacted]	[redacted]
Grade 2 (moderate)	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3 (severe)	[redacted]	[redacted]	[redacted]	[redacted]
Grade 4 (life-threatening or disabling)	[redacted]	[redacted]	[redacted]	[redacted]
Grade 5 (death)	[redacted]	[redacted]	[redacted]	[redacted]
TEAE by causality, n (%)				
Reasonable possibility	[redacted]	[redacted]	[redacted]	[redacted]

No reasonable possibility	[redacted]	[redacted]	[redacted]	[redacted]
Not applicable	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE: adverse event; BLV: bulevirtide; TDF: TEAE: treatment emergent adverse event; SAS: safety analysis set.

Notes: AEs were coded according to MedDRA Version 24.0. TEAEs began on or after the drug start up date up to 30 days after permanent discontinuation of the study drug, or led to premature study drug discontinuation. For the delayed treatment group, TEAEs began on or after the randomisation date up to the Week 48 visit date, or up to study discontinuation date if discontinued study before the Week 48 visit.

Source: Table 30, CSR.

Table 60. Adverse events occurring in at least 5% of participants in any group (MYR 301 safety set, reproduced from Table 29 of the CS)

AE by Preferred Term	Delayed Treatment (n=51)	BLV 2mg (n=49)	BLV 10mg (n=50)
Subjects with any TEAE, n (%)	[redacted]	[redacted]	[redacted]
Vitamin D deficiency	[redacted]	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]
Eosinophilia	[redacted]	[redacted]	[redacted]
ALT increased	[redacted]	[redacted]	[redacted]

Anaemia	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]
Abdominal pain upper	[redacted]	[redacted]	[redacted]
Injection site reaction	[redacted]	[redacted]	[redacted]
Proteinuria	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]
Injection site erythema	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]
Injection site pruritus	[redacted]	[redacted]	[redacted]
AST increased	[redacted]	[redacted]	[redacted]
Injection site swelling	[redacted]	[redacted]	[redacted]
Sleep disorder	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]
Bradycardia	[redacted]	[redacted]	[redacted]

Abbreviations: AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BLV: bulevirtide; SAS: safety analysis set; TEAE: treatment emergent adverse event.
Notes: Percentages are based on the number of participants treated with bulevirtide.
Source: Table 31, CSR

9.2 Natural history of disease

Table 61. Annual probabilities used by the company and EAG's proposed alternatives

Health State		Annual TP used in company's base case	Annual TP proposed by the EAG	Company's justification and EAG critique
From	To			
F2	F2+1 (up to F4)	15.1%	F2 to F3: 6.93% F3 to F4: 7.18%	The company reports taking a 5.3% estimate from Bermingham et al., 2016[41], which in its turn, reports taking the estimate from Fattovich 2003[42], where the cumulative incidence of cirrhosis in people with predominantly HBeAg positive CHB was reported to range from 8% to 20% over a five year period. The study reports taking the upper limit of the range and converting it into an annual probability of 5.3%. The company then multiplied this estimate by threefold as per Da[43], a literature review of the natural history of HDV (among other aspects of the disease) which concluded that patients co-infected with chronic HBV /HDV have a threefold risk of cirrhosis progression compared with HBV alone. The EAG considers that the Romeo et al. 2009 study is more appropriate as it includes estimates of progression from the different METAVIR stages to the compensated cirrhosis stage in on HDV positive patients. [2]
F2	HCC	1.38%	0.04%	The company used the Hsu et al. 2002[39] study to estimate the probability of F2 patients developing HCC. Hsu et al. only included patients with spontaneous HBeAg seroconversion, who had not received any previous treatment. Therefore, the population in the study consists of a niche group of patients, and crucially cannot be considered to represent a NR population. Furthermore, the paper reported that 3 out of 68 patients had HCC (which is the estimate used by the company in the analysis), however, 14 patients also had new cirrhosis, with 6 patients having cirrhosis at baseline. It is, therefore, not possible to know if the patients developing HCC were the same patients who also had cirrhosis, thus rendering this study not appropriate to estimate the probability of F2 non-responding patients developing HCC. The EAG considers that a more robust method for estimating the probability of HCC for the F2 and the F3 states would be to use the probability of HCC from the compensated cirrhosis stage from the Romeo study[2], and work backwards to calculate the probability of HCC in lower F-stages by using the HR from Kushner[3] of 5.2.
F3	HCC	2.86%	1.10%	The company used the Dienstag et al. paper to estimate the probability of F3 patients developing HCC by taking the relative risk between all clinical events reported in the study for patients with fibrosis (3.3%) and patients with cirrhosis (7.5%) at baseline. Even though the company did not provide details on the calculations undertaken, the EAG believes that the

				company applied the 0.44 risk decrease (3.3% divided by 7.5%) to the TP used to estimate the transition between F4 to HCC in the model (6.24%). Nonetheless, the company ignored the specific estimate for HCC in the study, which reported that fibrosis patients had 1.1% of HCC while cirrhosis patients had 2.4% (no statistical analysis was undertaken in the study). Furthermore, the study assessed outcomes for patients with advanced bridging fibrosis (Ishak fibrosis stage 3-4) or cirrhosis (Ishak stage 5-6). The Ishak fibrosis stage 3-4 correspond to METAVIR stages F2 or F3, while the Ishak stages 5-6 correspond to F3 of F4. Therefore, the alignment of the categories of fibrosis vs cirrhosis in the study with the METAVIR stages used in the model is not perfect, given that the fibrosis and the cirrhosis groups in the study both included F3 patients. Finally, the study was conducted in patients with chronic hepatitis C who had failed to achieve a sustained virologic response after a course of at least 12 weeks of interferon-based therapy. The company did not provide any justification for why the outcomes observed in HCV would be applicable to patients with HBV or HDV. The EAG considers that a more robust method for estimating the probability of HCC for the F2 and the F3 states would be to use the probability of HCC from the compensated cirrhosis stage from the Romeo study[2], and work backwards to calculate the probability of HCC in lower F-stages by using the HR from Kushner[3] of 5.2.
CC (F4)	HCC	6.24%	5.61%	The company took the 2.3% annual transition from the Bermingham et al., 2016[41] (a cost-effectiveness study in CHB) to estimate the transition between F4 and HCC. In order to adjust the disease rate to HDV patients, the company then increased the risk of HCC by 2.77 as per Alfaiate et al., 2020[38] (which reported a 2.77 higher risk of HCC for HDV infection vs. HBV monoinfection), resulting in a probability of HCC per year of 6.24% for patients with compensated cirrhosis. The EAG considers that a more robust method for estimating the probability of HCC for the F2 and the F3 states would be to use the probability of HCC from the compensated cirrhosis stage from the Romeo study.[2]
	DC	10.67%	14.67%	In order to estimate the probability of progression from F4 to a decompensated cirrhosis stage, the company used data from Dakin 2010[44] (a cost-effectiveness study in CHB) to obtain the annual transition probability of 5.0% to then increase it to represent faster progression in HDV patients using the 2.2 multiplier from Fattovich *et al*. 2000[8]. The EAG considers that a more robust method for estimating the probability of decompensation from the Romeo study.[2]

	Liver-Related Death	7.26%	Same as company's	Based on the 5-year survival probability of 86% from Fattovich *et al*. 2003[42] and increased by twofold as per Fattovich *et al*., 2000[8].
DCC	HCC	7.83%	Same as company's	The company reports taking the 2.3% estimate of HCC from Bermingham *et al.,* 2016 (a cost-effectiveness study in CHB in the UK)[41] and multiplying it by 2.77 to increase the risk of HCC as per Alfaiate *et al.*, 2020[38]. However, the EAG notes that this would result in 6.37%, and not 7.83%. The EAG recommends that the company clarifies this issue during technical engagement.
	LT	1.55%	Same as company's	The company took the 1.55% estimate of HCC from Bermingham *et al.,* 2016, which reported that the annual probability of a patient with DC or HCC undergoing liver transplant in the UK is 1.55%[41]
	Liver-Related Death	15.60	Same as company's	The company took the estimate from Bermingham *et al.,* 2016.[41]
HCC	LT	1.55%	1.55%	The company took the 1.55% estimate of HCC from Bermingham *et al.,* 2016, which reported that the annual probability of a patient with DC or HCC undergoing liver transplant in the UK is 1.55%[41]
	Liver-Related Death	56.00%	23.3%.	This value was used both in Bermingham *et al.,* 2016, and in Veenstra *et al*., 2007[61], both cost-effectiveness studies in CHB set in the UK. Both studies seem to have sourced this estimate from Wong et al. 1995. The EAG notes that in TA153 for entecavir the TP accepted for modelling the probability of death from the HCC state was 23.3%. Therefore, the EAG conducted a scenario analysis using this estimate, however the impact on the ICER was negligible.
LT	Liver-Related Death	21.00%	Same as company's	This value was used both in Bermingham *et al.,* 2016, and in Veenstra *et al*., 2007[61], both cost-effectiveness studies in CHB set in the UK.
Post-LT	Liver-Related Death	5.70%	Same as company's	This value was used both in Bermingham *et al.,* 2016, and in Veenstra *et al*., 2007[61], both cost-effectiveness studies in CHB set in the UK.

Single Technology Appraisal

EAG report – factual accuracy check and confidential information check

Bulevirtide for treating chronic hepatitis D [ID3732]

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 18 July 2022** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 Incorrect data

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Table 13, Section 3.3.1 (page 49), the median (IQR) change from baseline in HDV RNA levels at Week 4 has been inputted as [redacted]	Please correct the median (IQR) change from baseline in HDV RNA levels at Week 4 in Table 13 to [redacted] as specified in Table 14.2.3.3-19 in the MYR 301 CSR.	Alignment with Table 14.2.3.3-19 in the MYR 301 CSR.	Thank-you for highlighting this. The EAG report has been corrected.

Issue 2 Incorrect table citation

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
In the Table 13 legend Page 49, CSR Tables 14.2.3.3-19 and 14.2.3.4-7 were cited as sources for the data regarding change from baseline in HDV RNA and ALT levels While Table 14.2.3.3-19 is the correct source for the change from baseline in HDV RNA levels, Table 14.2.3.4-7 is incorrectly cited as a source of information for the change from baseline in ALT levels.	Table 14.2.3.4-9 is the correct table to be cited for the change from baseline in ALT levels.	Correct source for the change from baseline in ALT levels.	Thank-you for highlighting this. The EAG report has been corrected.

In Section 3.3.5 Page 55, the EAG states: 'Bile salt elevations above the ULN, an AE that is expected to occur because bulevirtide inhibits the bile acid transporter (the sodium taurocholate cotransporting polypeptide), were not reported as AEs for MYR 301 if they were asymptomatic and judged by the investigator to be clinically insignificant, but the change from baseline in total blood bile salts for the MYR 301 arms were reported in Table 13.3.3-1 of the CSR: in the delayed treatment arm, total bile salts had reduced by a median of -2.80 (IQR: 9.80) at Week 48, compared to baseline, whereas they had increased by 5.50 (IQR: 20.00) in the bulevirtide 2 mg arm.'	Table 14.3.3.3-1 is the correct source for the change in baseline in total blood bile salts for MYR 301.	Correct source for the change from baseline in total blood bile salts.	Thank-you for highlighting this. The EAG report has been corrected.

Issue 3 METAVIR fibrosis staging

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Section 3.3.3 Page 54, the EAG notes that: 'METAVIR fibrosis staging data at both baseline and Week 48 were available for [redacted] of MYR 301 participants.'	We propose that the text should be amended to the following: METAVIR fibrosis staging data at both baseline and Week 48 were available for [redacted] of patients in both the BLV 2 mg and delayed treatment arms.	Inaccurate reporting of METAVIR fibrosis staging data from MYR 301.	Thank-you for highlighting this. The wording in the EAG report has been updated to: METAVIR fibrosis staging data at both baseline and Week 48 were available for [redacted] of patients across the bulevirtide 2 mg and delayed treatment arms of MYR 301.

Issue 4 Clarification regarding EAG request for additional analyses

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Section 8.2.2 Page 64, the EAG state: 'The company did not undertake the analysis and therefore the EAG asks that the company reconsiders this at technical engagement'	We propose that the text should be amended to the following: Due to time constraints (the short time between receipt of clarification questions and the deadline for response) it was not feasible for the Company to undertake the analysis, therefore the EAG asks that the Company reconsiders this at technical engagement.	Clarification for the reasoning why this requested analysis was not provided.	Not a factual inacurracy.

Issue 5 Response assesments within the model

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Section 8.2.7.1 Page 69: Patients had their first assessment of response at 48 weeks in the model to determine treatment continuation in the model.	Patients had their first assessment of response at 24 weeks in the model. The first response assessment to determine treatment continuation was however at week 48 in the model.	Clarification regarding the timepoints at which patients' response to treatment is reported within the model.	Thank-you for highlighting this. For clarity the wording has been updated to: Patients had their first assessment of response to determine treatment continuation in the model at 48 weeks.

Issue 6 Extrapolation of biochemical response

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 8.2.7.2 Page 73, the EAG state: 'During clarification, the EAG noted that the fitted curves with the EMAX function used by the company only provided a plausible fit to the observed data for virologic response, while the extrapolated curves for biochemical response were a poor fit (doted orange curves in Figure 4 and Figure 5, for bulevirtide and BSC, respectively) to the observed data (dotted blue curves in in Figure 4 and Figure 5, for bulevirtide and BSC, respectively). Therefore, the EAG asked that the company reconsidered the fitted curves used in the model'	The text should be ammended to clarify that the extrapolations for biochemical response, whilst included as an option within the model, are not used in the company base-case or any of the scenarios applied in the company submission, nor the revised post-clarification base-case. We propose that the text should be ammended to the following: During clarification, the EAG noted that the fitted curves with the EMAX function used by the company only provided a plausible fit to the observed data for virologic response, while the extrapolated curves for biochemical response were a poor fit (dotted orange curves in Figure 4 and Figure	Potentially misleading representation of the company base-case.	Not a factual inaccuracy. The EAG does not state that the biochemical response curves alone are included in the model and also adds a paragraph at the end of page 75 stating "*Nonetheless, the EAG acknowledges that only one data point (for each treatment arm) resulting from the company's extrapolation exercise is used in the economic model. This consists of the TP from the PR to the CR states at week 72 in the bulevirtide arm (34%) and in the BSC arm (5.32%)*."

	5, for bulevirtide and BSC, respectively) to the observed data (dotted blue curves in in Figure 4 and Figure 5, for bulevirtide and BSC, respectively). The EAG notes that the extrapolated data for biochemical response is not however used in the model base-case or any of the scenarios provided by the company, as it is only the extrapolated data for combined response and virologic response that is applied.		

Issue 7 Antiviral medication usage in economic model

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 8.2.10.10 Page 94: the EAG states 'the company assumed that 60% of patients are given an antiviral treatment (tenofovir 245 mg) for underlying HBV infection'	Suggested to correct to: Based on the proportion of antiviral usage reported in MYR 301, the company assumed that 60% of patients are given an antiviral treatment (tenofovir 245 mg) for underlying HBV infection.	Clarification of source of 60% estimate for antiviral medication use.	This has been updated to: …the company assumed that 60% of patients are given an antiviral treatment (tenofovir 245 mg) for underlying HBV infection, based on the proportion of antiviral usage reported in MYR 301.

Issue 8 Calculating error

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.1.1 Page 32: the EAG states [redacted]	Suggested to correct to: [redacted]	Calculating error. Alternatively the EAG may be referring to the percentage with METAVIR staging performed at both baseline and Week 48.	Thank-you for highlighting this. The EAG report has been corrected.

Issue 9 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 15: the EAG states 'Sections 1.3 explain'	Suggested to correct to 'Section 1.3 explains'	Typographical error.	Thank-you for highlighting typographical errors throughout the document. This has been corrected in the EAG report.
Page 15: the EAG states 'which in in'	Suggested to correct to 'which in'	Typographical error.	Corrected.
Page 19: the EAG defines the abbreviation LT as 'lung transplant'	Suggested to correct to 'liver transplant'	Inaccurate definition.	Corrected.
Page 24: the EAG states 'Treatments for underlying CHB include nucelos(t)ide analogues (NAs), such as tenofovir disoproxil and entecavir are used in UK practice.'	Suggested to correct to 'Treatments for underlying CHB include nucelos(t)ide analogues (NAs), such as tenofovir disoproxil and entecavir, which are used in UK practice.'	Typographical error.	Updated.
Page 31: the EAG states 'The EAG's clinical experts note that in practice liver biopsies are always discuss with patients'	Suggested to correct to 'The EAG's clinical experts note that in practice liver biopsies are always discussed with patients'	Typographical error.	Corrected.

Page 32 & elsewhere, the EAG refer to 'biological response'	Suggested to consistently refer to as 'biochemical response'	Typographical error.	Corrected on page 32 and page 50.
Page 33: the EAG refer to 'prior IFN treatment'	Suggested to consistently refer to as 'prior IFN-based therapy'	Typographical error.	Updated on pages 29, 33 and 37.
Page 34: the EAG refer to 'reliance model'	Suggested to correct to reliance route or procedure	Incorrect name.	Corrected to reliance procedure.
Page 38, the EAG refer to the active substance as 'bulveritide'	Suggested to correct to 'bulevirtide'	Typographical error.	Corrected.
Page 39: the EAG state 'interferon (IFN)-based therapies'	Suggested to correct to 'IFN-based therapies'	Interferon was spelled out earlier in the report.	Not a factual inaccuracy. The EAG restates abbreviations in each major section.
Page 40: the EAG refer to 'MYR 2020'	Suggested to correct to 'MYR 202'	Typographical error.	Corrected.
Page 44, the EAG state 'overestimation of the rate ALT normalisation.'	Suggested to correct to 'overestimation of the rate of ALT normalisation.'	Typographical error.	Corrected.
Page 51: the EAG refer to 'they likely to be closer'	Suggested to correct to 'they are likely to be closer'	Typographical error.	Corrected.
Page 56: the EAG state 'This contributed to a total of [redacted] participants ([redacted]) experiencing a potential hepatic flare in [redacted] delayed	Suggested to correct to 'This contributed to a total of [redacted] participants [redacted] experiencing a potential hepatic flare in the delayed treatment arm, compared with [redacted]	Multiple typographical errors. Markup is also added, as described in the incorrect marking table below.	Thank-you for highlighting this. The typographical errors have been fixed and correct mark-up added.

treatment participants and [redacted] participants ([redacted] in the bulevirtide 2 mg arm. Eosinophilia was reported in [redacted] participants in the bulevirtide 2 mg arm, but in no participants in the delayed treatment arm.'	participants ([redacted] in the bulevirtide 2 mg arm. Eosinophilia was reported in [redacted] participants in the bulevirtide 2 mg arm, but in no participants in the delayed treatment arm.		
Page 64: the EAG state 'The resulting baseline distribution used by the company was 60% of F4 patients; 24% of F3 and 16% of F2 patients.'	Suggested to correct to 'The resulting baseline distribution used by the company was 60% of F4 patients; 24% of F3 and 17% of F2 patients.'	Incorrect value specified for proportion of F2 patients, due to a rounding error.	Corrected to 17% of F2 patients.
Page 65: the EAG state 'assumed to be 46% in company's calculations'	Suggested to correct to 'assumed to be 46% in the company's calculations'	Typographical error.	Corrected.
Page 65: the EAG state 'The company also used Spaan et al. to inform baseline age in the model (35.1 years)'	Suggested to remove double-spacing, correcting to 'The company also used Spaan et al. to inform baseline age in the model (35.1 years)'	Double-spacing.	Double-space removed.
Page 65: the EAG state 'Given the considerable impact that baseline age and cirrhosis distribution has on the'	Suggested to correct to 'Given the considerable impact that baseline age and cirrhosis distribution have on the'	Grammatical error.	Corrected.

Page 66: the EAG state 'model was 24 weeks was the model was based on a'	Suggested to correct to 'model was 24 weeks as the model was based on a'	Typographical error.	Corrected.
Page 67: the EAG state 'mean age in the at baseline was assumed to be 35 years'	Suggested to correct to 'mean age in the model at baseline was assumed to be 35 years'	Typographical error and double-spacing.	Corrected.
Page 69: the EAG state 'response to treatment at 24 and the 48 weeks in the model.'	Suggested to correct to 'response to treatment at 24 and 48 weeks in the model.'	Typographical error.	Corrected.
Page 70: the EAG state 'two scenarios analysis in the model'	Suggested to correct to 'two scenario analyses in the model'	Typographical error.	Corrected.
Page 73: the EAG state 'doted orange curves in Figure 4'	Suggested to correct to 'dotted orange curves in Figure 4'	Typographical error.	Corrected.
Page 73: the EAG state 'The EAG considers the company's scenario analysis flawed'	Suggested to correct to 'The EAG considers the company's scenario analyses flawed'	Typographical error.	Corrected.
Page 79: the EAG state 'The Fattovich et al. 2000 study'	Suggested to correct to 'The Fattovich et al. 2000 study'	Double-spacing.	Double-space removed.
Page 81: the EAG state 'then multiplied 5.3% estimate'	Suggested to correct to 'then multiplied the 5.3% estimate'	Typographical error.	Corrected.

Page 81: the EAG state ‘This compares to the 15.1% used by the company from every fibrosis stage.’	Suggested to correct to ‘This aligns with the 15.1% used by the company from every fibrosis stage.’	Unclear narrative, needing clarification on how exactly the figures compare with each other.	Not a factual inaccuracy. The EAG is comparing the 15.1% probability used by the company with the Romeo estimate of 0.8%
Page 82: the EAG state ‘however, these provide an alternative’	Suggested to correct to ‘however, these estimates provide an alternative’	Typographical error.	Updated.
Page 83: the EAG state ‘study also suggest that HCC’	Suggested to correct to ‘study also suggests that HCC’	Typographical error.	Corrected.
Page 86: the EAG state ‘with viral suppression of’	Suggested to correct to ‘with viral suppression of’	Double-spacing.	Double-space removed.
Page 89: the EAG state ‘performed to identified relevant’	Suggested to correct to ‘performed to identify relevant’	Typographical error.	Corrected.
Page 91: the EAG state ‘The EAG notes that’	Suggested to correct to ‘The EAG notes that’	Double-spacing.	Double-space removed.
Page 91: the EAG state ‘patients in the PLT were’	Suggested to correct to ‘patients in the PLT state were’	Typographical error.	Corrected.
Page 94: the EAG state ‘The SmPC for’	Suggested to correct to ‘The SmPC for’	Double-spacing.	Double-space removed.
Page 94: the EAG state ‘Regardless, the SmPC for’	Suggested to correct to ‘Regardless, the SmPC for’	Double-spacing.	Double-space removed.

Page 110: the EAG state ‘and to £64,765 when’	Suggested to correct to ‘and to £64,765 when’	Double-spacing.	Double-space removed.
Page 114: the EAG state ‘The results of the EAG’s QALY shortfall analysis is presented’	Suggested to correct to ‘The results of the EAG’s QALY shortfall analysis are presented’	Typographical error.	Corrected.
‘Evidence Assessment Group (EAG)’ is repeated three times	Suggested to provide the full term and abbreviation once, followed by EAG throughout	Typographical error.	Not a factual inaccuracy. The EAG repeats abbreviations for each major section.
National Institute for Health and Care Excellence (NICE) is repeated twice	Suggested to provide the full term and abbreviation once, followed by NICE throughout	Typographical error.	Not a factual inaccuracy. The EAG repeats abbreviations for each major section.
The model’s decompensated cirrhosis health state is abbreviated to ‘DC’ by the EAG, but is abbreviated to ‘DCC’ in the CS.	Suggest that all references to the ‘DC’ health state are changed to ‘DCC’ for consistency	Typographical error.	Not a factual inaccuracy.

Issue 10 Non-synched cross-references

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 67: the EAG state 'Please refer to Section 0 for further details on how health state transition probabilities were implemented in the model'	Update the cross-reference to the appropriate section that the EAG wish to refer to.	Error with cross-references.	Thank-you for highlighting this. The correct section number (4.2.5) has been added.
Page 67: the EAG state 'extrapolating treatment effectiveness in the model in Section 0'	Update the cross-reference to the appropriate section that the EAG wish to refer to.	Error with cross-references.	Thank-you for highlighting this. The correct section number (4.2.5) has been added.

Issue 11 Incomplete references

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 80: the EAG state 'the Fattovich or the Romeo studies'	Suggested to provide the year of publication and 'et al.' for the in-text citation of these studies.	Incomplete referencing, there are mutliple Fattovich et al., studies for example that have been used in the CS thus it would be helpful to clarify .	Thank-you for pointing out this uncertainty. These have been updated to Fattovich et al. 2000 and Romeo et al. 2009 throughout this section.
Page 81: the EAG state 'as per Da, a literature review of the natural history of HDV'	Suggested to correct to: as per Dakin et al., 2010 , a literature review of the natural history of HDV	Reference incomplete as author name is cut off.	Da is the correct author name for this reference. It has been updated to read Da et al. 2019 to avoid any confusion.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Bulevirtide for treating chronic hepatitis D [ID3732]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **2 September 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Technical engagement response form

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Gilead Sciences Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None.

Introduction

Gilead would like to thank the NICE technical team for reviewing the company submission for bulevirtide for the treatment of hepatitis delta, preparing the technical report, and for providing us with the opportunity to engage in the technical engagement process.

Our response is split into four separate parts:

1) Company response to the four key issues identified in the EAR
2) Company response to the additional issues raised by the EAG
3) Details of the revised company base case in response to the EAR
4) Additional supportive evidence, provided as a technical appendix

Gilead acknowledge the uncertainty in the extrapolations of the MYR 301 efficacy data that were highlighted within the EAR. To address the uncertainty associated with the original extrapolations, we have explored alternative methods of extrapolating the MYR 301 efficacy data. This is discussed in detail in the response to key issue 3 and has been included within this response document as additional supportive evidence. Further details regarding the extrapolation methodology are submitted as part of a supplementary technical appendix.

1. Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Generalisability of trial population to the narrower population focused on by the company	Yes	**The overall MYR 301 trial population is likely to be IFN-based therapy experienced, intolerant, or contraindicated and is therefore reflective of the position adopted in the CS** The Evidence Assessment Group (EAG) highlighted that it was unclear as to what proportion of patients enrolled in the pivotal MYR 301 study were contraindicated or ineligible for treatment with interferon-based therapy (hereafter referred to as IFN-based therapy), and therefore queried the generalisability of the trial population with the narrower population specified in the decision problem. In the full trial population of the MYR 301 clinical study, 56.0% of subjects had received prior treatment with IFN-based therapy. Treatment guidelines for the management of hepatitis B virus (HBV)/hepatitis delta virus (HDV) co-infection recommend treatment with peginterferon alfa-2a (PEG-IFN), and it is expected to be offered to almost all chronic hepatitis delta (CHD) patients with compensated liver disease (1,2). As such, it is considered likely that patients who had not received prior IFN-based therapy at baseline were not offered this treatment as they were either contraindicated or unlikely to tolerate treatment. These patients would therefore fall within the proposed population in the company submission (CS). This is supported by the EAG's clinical experts, who highlighted that '*the limitations of PEG-IFN treatment mean that a substantial portion of patients with CHD, compensated liver disease and significant fibrosis are not offered treatment with PEG-IFN as they are either contraindicated or are unlikely to tolerate treatment.'*

		On this basis, whilst Gilead acknowledge that in the absence of recorded data the percentage of patients who were not offered IFN-based therapy due to intolerance or contraindication is not defined, we propose that this is likely to be almost all patients who had not received prior IFN-based therapy at baseline. **Combined response is the key driver of the model** The EAG hypothesise that it may *potentially* be easier for patients with a lower METAVIR fibrosis stage (F0 or F1) to achieve biochemical response, which if true could lead to an overestimate of efficacy in the bulevirtide 2 mg treatment arm versus best supportive care (BSC) in the full trial population. However, the model is driven by the achievement of a combined response, which requires the fulfilment of a biochemical response and a virologic response. A virologic response was defined as undetectable (< limit of detection [LoD]) HDV ribonucleic acid (RNA) or decrease by ≥2-$\log_{10}$ IU/mL from baseline at Week 48. It is also worth noting that in contrast to alanine aminotransferase (ALT) normalisation, the percentage of patients achieving a virologic response in the bulevirtide 2 mg treatment arm was greater in the subgroup of patients with cirrhosis ([redacted] of 23 patients) compared to the non-cirrhotic subgroup ([redacted] of 26 patients) (3). **The cirrhotic subgroup includes significant amounts of missing data** The EAG recommended that a scenario analysis focusing on the cirrhotic subgroup of patients in MYR 301 was included within the model. In lieu of response data by METAVIR fibrosis stage, the EAG considered this scenario to be the best proxy for estimating the contribution of participants with METAVIR stages F0 or F1 to the overall study results. Whilst Gilead acknowledges a slight imbalance between treatment arms with regards to proportion classified as METAVIR fibrosis stages F0 or F1 in the overall population, constituting [redacted] of patients ([redacted] of 49 patients) in the bulevirtide 2 mg treatment arm and [redacted] of patients ([redacted] of 51 patients) in the delayed treatment arm, we would challenge the EAG's preference for the cirrhotic subgroup as a more appropriate proxy. In the pivotal MYR 301 clinical study, liver biopsies were not a requirement for trial inclusion, and the EAG's clinical experts note in Section 2.3.1 of the technical report that liver biopsy is always discussed with patients likely to have advanced liver disease, but often not favoured by patients due

to the invasive nature of the procedure. As presented in Table 1.1, for the cirrhotic subgroup data on fibrosis stage was only available for [redacted] of patients ([redacted] of 24 patients) in the delayed treatment arm and [redacted] of patients ([redacted] of 23 patients) in the bulevirtide 2 mg treatment arm.

Furthermore, whilst the numbers classified as METAVIR fibrosis stage F0 or F1 are balanced between arms, the proportion of these amongst those with data available are imbalanced. Of those with biopsy performed at baseline, [redacted] of patients ([redacted] patients) in the delayed treatment arm, and [redacted] of patients ([redacted] patients) in the bulevirtide 2 mg arm were classified as METAVIR fibrosis stages F0 or F1. With the additional confounder of missing data for [redacted] of the cirrhotic subgroup as described in the previous paragraph, Gilead do not consider this proxy to be a preferable approach to using the full trial population.

Table 1.1: METAVIR fibrosis scores at baseline of MYR 301 cirrhotic participants

Arm	METAVIR fibrosis score at baseline					
	F0	F1	F2	F3	F4	Missing
Cirrhotic participants						
Delayed Treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bulevirtide 2 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

As requested by the EAG, an exploratory scenario analysis using the cirrhotic subgroup response data applied to the F2-F4 population was run in the model. Efficacy data for the cirrhotic subgroup were available for up to Week 48 of MYR 301 and thus virological and composite response was taken from the clinical study report (CSR) for the cirrhotic and non-cirrhotic subgroup. The proportion of responders in the cirrhotic and non-cirrhotic subgroups was weighted based on the proportion of non-cirrhotic to non-cirrhotic patients at baseline within the model. For the extrapolated timepoints within the model (72 and 96 weeks), we modelled response for the cirrhotic/non-cirrhotic subgroup by assuming the same relative increase in response from extrapolating as observed in the overall

<table>
<tr>
<td></td>
<td></td>
<td>population. The results for this scenario are presented in Table 1.2 below, compared with our updated company base case (see Table 4 and Issue 2).

Table 1.2: Scenario analysis results using cirrhotic subgroup response rates from MYR 301
<table>
<tr><th>Interventions</th><th>Incremental costs (£)</th><th>Incremental LYG</th><th>Incremental QALYs</th><th>ICER (£/QALY)</th><th>Base-case ICER[1]</th></tr>
<tr><td colspan="6">Results without severity modifier</td></tr>
<tr><td>BSC</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Bulevirtide</td><td>[redacted]</td><td>5.28</td><td>[redacted]</td><td>£40,657</td><td>£39,691</td></tr>
<tr><td colspan="6">Results including severity modifier of 1.2</td></tr>
<tr><td>BSC</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Bulevirtide</td><td>[redacted]</td><td>5.28</td><td>[redacted]</td><td>£33,881</td><td>£33,076</td></tr>
</table>
Note 1: Updated company base case, see Table 4 and Issue 3.

This exploratory scenario analysis shows that removing the perceived imbalance between treatment arms in terms of METAVIR fibrosis stage, by assessing the treatment effect of bulevirtide based on the balanced cirrhotic subgroup, has only a marginal impact on the ICER.</td>
</tr>
<tr>
<td>Key issue 2:
Generalisability of trial population to UK patients</td>
<td>Yes</td>
<td>Baseline characteristics from external UK-specific literature sources are more appropriate for the economic model

Although the pivotal MYR 301 clinical study did not enrol any patients from the UK, it represents the best source of clinical efficacy and safety data regarding the treatment of CHD with bulevirtide compared to best supportive care. The pivotal Phase 3 MYR 301 study enrolled 150 patients across 16 study sites located across Russia (7 sites), Germany (5 sites), Italy (3 sites) and Sweden (1 site). The average age of participants in the full trial population was 41.8 years, and 57.3% were male. Almost half of the participants (47.3%) had cirrhosis at the time of enrolment based on investigator assessment.</td>
</tr>
</table>

In the absence of UK clinical trial sites in the pivotal study, baseline characteristics from Spaan *et al*., (2020), who carried out a long-term retrospective analysis of 107 CHD patients in the UK population, were used to inform the economic model. Compared to MYR 301, a lower mean age of 35.1 years was observed in the actively replicating HDV patient population, comprising 46 patients in total. Furthermore, 58.7% of these participants were male and 50.0% of patients with actively replicating HDV had cirrhosis (4).

The EAG's clinical experts consider that '*while the baseline characteristics included in the company's model were representative of the UK population, the baseline characteristics in the trial were not clinically implausible'*. Gilead notes that the EAG's clinical experts are aligned with the use of baseline characteristics from Spaan *et al*., (2020) in the economic model. Whilst we also acknowledge the experts considered that the baseline characteristics from MYR 301 are 'not clinically implausible', this appears to be a relatively weak endorsement compared to the UK-specific study conducted by Spaan *et al*., (2020). UK clinical experts have advised Gilead that it is appropriate to utilise the Spaan *et al.,* (2020) study for baseline demographic data. Furthermore, the EAG have not provided any evidence from their clinical experts to say that the Spaan *et al.,* (2020) study is inappropriate.

As recommended by the EAG, Gilead have presented available data from the literature regarding the typically presenting age and cirrhotic distribution of CHD patients in the UK in Table 2.1 below. The baseline age and proportion of cirrhotic patients published by Spaan *et al*., (2020) is supported by additional external literature sources.

Table 2.1: External literature sources for baseline age and cirrhotic status of CHD patients in the UK

Reference	Sample size (n)	Age (years)	Cirrhotic (%)
Cross *et al*., (2008) (5)	82	Median: 36.0	26.8
Tong *et al*., (2013) (6)	33	Mean: 35.4	59.1
El Bouzidi *et al*., (2015) (7)	55	Median: 40.0	49.0

		<table><tr><td>Jackson *et al*., (2018) (8)</td><td>23</td><td>Mean: 36.0</td><td>NR</td></tr><tr><td>Spaan *et al*., (2020) (4)</td><td>46</td><td>Mean: 35.1</td><td>50.0</td></tr><tr><td>Bigogno *et al*., (2020) (9)</td><td>16</td><td>Median: 37.0</td><td>NR</td></tr></table> Abbreviations: NR: not reported. Whilst not all publications report the cirrhotic status of patients, there appears to be a consensus of approximately 50.0%, based on data from Tong *et al.,* (2013), El Bouzidi e*t al*., (2015), and Spaan *et al*., (2020). A clinical expert attending a Gilead advisory board also highlighted that the proportion of patients with cirrhosis in the MYR 301 study population (47.3%) was lower than what they may expect for the UK CHD population (10). In conclusion, Gilead strongly stands by its approach of using baseline demographics from Spaan *et al*., (2020) in the economic model and believes that the use of this data source is supported by the EAG's clinical experts.
Key issue 3: Uncertainty in the extrapolations beyond the observed trial data	Yes	**Extrapolation of response rates using MYR 301 individual patient data (IPD)** We acknowledge the uncertainty in the extrapolations that were highlighted within the EAR. During technical engagement, Gilead have explored alternative methods of extrapolating the MYR 301 trial data. In the original submission, response rates were extrapolated based on aggregate data from MYR 301. We have therefore extrapolated the trial data using IPD which may be considered a more robust approach. IPD was used for the long-term extrapolation of 5 endpoints: - ALT (biochemical) response - HDV RNA decrease - HDV RNA undetectability - Virologic response - Composite response Based on the IPD, extrapolation was performed using nonlinear least squares (NLSE) regression, with a binomial link function. Compared to the EMAX approach, fitting the data to a parametric function using NLSE estimation is more flexible, since patients can be classified as responders or

		non-responders at each specific time-point, based on the distributional form of the patients at that time-point. An assessment of the suitability of each fitted model to the observed and predicted data was undertaking using several methods including visual inspection, statistical tests of relative fit, and by considering the clinical plausibility of the extrapolations. Internal validation was assessed by using Akaike Information Criterion (AIC) to assess the relative fit of the alternative parametric models including logistic, log-logistic, and Weibull. The log-logistic model provided a clinically plausible estimate and was considered the best parametric fit to the IPD. Other validation methods, such as cross-validation, were deemed inappropriate given the small sample size. Overall, the new extrapolation approach provides a more conservative fit to the data, compared to the EMAX approach, whilst still predicting a sustained and high response up to the extrapolated period of 76 to 92 weeks. For example, for the proportion of patients on bulevirtide 2mg, over the period of 4 to 48 weeks IPD: • The proportion of predicted combined and virologic responders using the log-logistic model using NLSE provides a much closer fit to the observed IPD than the EMAX model. Specifically, this is evident in Weeks 24 to 40, where the EMAX under-predicted the proportion of responders and then, at 48 weeks, over-predicted the results by an average of roughly 13% for both combined and virologic responders. Similar trends are observed in the EMAX model for the endpoint of HDV RNA undetectable. • In comparison, the log-logistic model using NLSE notably provides a much closer fit to the observed IPD whilst still predicting a high and sustained response across the 5 endpoints. In addition, for the proportion of subjects on delayed treatment: • The EMAX model under-predicts the proportion of patients showing combined response versus the observed data. In comparison, the log-logistic model using NLSE, for example, provides a much closer fit to the model all endpoints. Therefore, given these trends as well as the improved AIC scores and visual fits, the log-logistic model reduces extrapolation uncertainties. It is important to note that the primary limitation of using the NLSE method is that the estimated proportion of responders may become greater than 100%,

over a longer period of follow-up. Nevertheless, this limitation does not impact the predictions over a relatively short follow-up, such as the 72 or 96 weeks period used for this extrapolation, however it is an important consideration when implementing the IPD extrapolations into the cost-effectiveness analysis.

Incorporation of new extrapolations into cost-effectiveness model

The new set of extrapolations, based on MYR 301 IPD were incorporated into the cost-effectiveness model and are applied in the updated, post technical engagement company base-case which results in an ICER of £39,691. For comparison, the new company base case excluding the new extrapolations is presented below:

Table 3.1: Cost-effectiveness results, updated base-case with new method of extrapolating MYR 301 data

Interventions	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER excluding new extrapolation (£/QALY)	ICER[1] (£/QALY)
Results without severity modifier					
BSC	-				
Bulevirtide	[redacted]	5.46	[redacted]	£38,852	£39,691
Results including severity modifier of 1.2					
BSC	-				
Bulevirtide	[redacted]	5.46	[redacted]	£32,376	£33,076

Note 1: Updated company base case, see Table 4 for other changes.

		It is noteworthy that as per the original submitted base-case, extrapolated data are only used at Week 72 within the model. 96-week data from MYR 301 is expected in [redacted], which will aid in addressing the uncertainty in response rates beyond 48 weeks in the model.
Key issue 4: Modelling of HCC	Yes	**Clinician validation** As recommended by the EAG, Gilead sought to validate the assumptions around the way hepatocellular carcinoma (HCC) was modelled in the submitted cost-effectiveness model. A questionnaire was sent out via email to clinical experts based in the UK. The assumptions regarding the modelling of HCC, in particular the possible health state transitions from this state were outlined, followed by a set of questions asking the experts to state whether the model's assumptions were realistic, whether cure was a clinical reality for CHD patients and if yes, the proportion of patients that they would estimate to be cured or progression-free from HCC. 2 leading clinical experts in the UK provided advice. Of note, one of the clinical experts stated that the proportion of CHD patients eligible for procedures such as resection or ablations (which the EAR states can be curative in HCC) is very low, approximately 10% to 20%, as most CHD patients have significant portal hypertension. With regards to proportions achieving cure, both KOLs stated that this would be a very small number of patients, approximately 30%. **Scenario including cure for HCC patients** As recommended by the EAG, we have updated the cost-effectiveness model to include a scenario where a proportion of HCC patients can transition to a progression-free state of the disease. This has been implemented by including a cell in the settings sheet, specifying the proportion of HCC patients who are assumed to be cured. The proportion cured is assumed to have both a higher utility value and lower mortality rate than uncured patients, with overall utility and mortality rates for HCC patients calculated as a weighted average of cured and uncured values. There is a scarcity of published data on the proportions of cure in HCC patients who had CHD. In line with the feedback received from clinical experts, we assumed a proportion of 30% cure for this scenario and implemented this by reducing excess mortality from HCC by 30% and adjusting the health state utilities for cured HCC patients as follows:

- For those patients who remain uncured, the original health state utility of 0.52 is applied, whilst for the proportion who are cured, a utility of 0.70 is applied. The 0.70 utility value was sourced from the PFS health state utility value that was applied for the standard of care arm in NICE TA688 (Selective internal radiation therapies (SIRT) for treating HCC) (11).

As can be seen in the table below, this scenario analysis had a marginal impact on the ICER; the cure assumption did not increase the ICER substantially compared to the revised, post-technical engagement company base-case ICER (£39,913 vs. £39,691 per QALY).

Table 4.1: Cost-effectiveness analysis results for scenario where 30% of HCC patients are assumed cured

Interventions	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER[1] (£/QALY)	Base-case ICER[1]
Results without severity modifier					
BSC				-	-
Bulevirtide	[redacted]	5.50	[redacted]	£39,913	£39,691
Results including severity modifier of 1.2					
BSC				-	-
Bulevirtide	[redacted]	5.50	[redacted]	£33,261	£33,076

Note 1: Updated company base case, see Table 4 and Issue 3.

2. Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Assuming that 48 weeks is the maximum timeframe for assessing final response to treatment, and treatment effectiveness is not extrapolated e.g., assume response rates do not improve beyond Week 48.	Section 4.2.4.1, pages 67-68	No	In the company base-case, observed MYR 301 response rates inform modelled response rates at Weeks 24 and 48. As stated in the original CS, although the available follow-up data from MYR 301 are limited to 48 weeks, analysis of the individual patient data (IPD) indicates that response rates were still increasing at that timepoint. A clear trend can be observed which shows that virologic and combined response rates are increasing over time. Therefore, the proportion of complete responders among those remaining on treatment past 48 weeks is expected to increase. The response rates for the 2mg bulevirtide and delayed treatment arms of MYR 301 up until week 48 were therefore extrapolated to estimate treatment response at Weeks 72 and 96. The EAG's preferred base-case assumes that 48 weeks is the maximum timeframe for assessing final response to treatment with bulevirtide: efficacy data from MYR 301 are not extrapolated, that is, it is assumed that response rates do not

			improve beyond Week 48. The company provided this as a scenario in the original CS (see Section B.3.11, pages 157-159). Gilead disagree with the EAG's statement that limiting the timeframe for assessing response to 48 weeks is a more robust method compared to the extrapolation of efficacy data. A clear trend of improving response rates can be observed in the data. Furthermore, extrapolations are only applied in the model until Week 72, which is a conservative assumption and is not clinically implausible. Functionality is provided in the model to explore the impact on the ICER of assessing response (partial and complete) at week 96. As stated in the original CS, the Week 48 assessment can be considered an early assessment of efficacy that evaluates achievement of a virologic response (HDV-RNA undetectability or ≥2-$\log_{10}$ decline) while the Week 72 assessment can be considered a definitive assessment of both virologic and biochemical response (MYR 301 primary endpoint; composite response of HDV-RNA undetectability or 2-$\log_{10}$ decline and ALT normalisation at Week 48). Having these two continuation rules allows sufficient time for patients to achieve a clinical response (given that response rates were still increasing at Week 48 in MYR 301). In other words, at Week 48 the model evaluates both virologic and biochemical response as per the MYR 301 primary endpoint. Those who fail to show virologic response are classified as non-responders and discontinue bulevirtide. However, the model applies a definitive assessment of the composite endpoint at Week 72 for patients that had achieved the virologic response

			to allow sufficient time for patients to achieve ALT normalisation and therefore, clinical response as defined by the composite endpoint (virologic and biochemical response) as in MYR 301. The EAG's clinical expert feedback that 'response (or lack thereof) to treatment is assessed well before 48 weeks, at 3 or 6 months' is not aligned with the feedback Gilead received from. Clinicians attending an advisory board stated that they preferred 48 weeks over 24 weeks as a timepoint for the stopping rule within the model. It was widely agreed that 24 weeks was not the optimal time to take a view of the efficacy of bulevirtide. Clinicians were aligned on a stopping rule at 48 weeks if patients were not responding with bulevirtide. A timepoint of 3 to 6 may also be considered too premature to assess response given the NICE clinical guideline for chronic hepatis B which states that clinicians should *'Consider stopping peginterferon alfa-2a if there is no decrease in HDV RNA after 6 months to 1 year of treatment. Otherwise, continue treatment and re-evaluate treatment response annually'.* Additionally, the EAG's opinion is in contrast to the SmPC which states: 'treatment should be continued as long as associated with clinical benefit'.
Additional issue 2: Estimation of the probability of hepatocellular carcinoma (HCC) from the F2-F4 states according to Romeo and Kushner	Table 25, Section 4.2.5.3.1., page 78	No	In the cost-effectiveness model, the natural history of CHD was modelled using estimates sourced from published literature. The EAR states that *'the EAG is concerned that the company did not provide a robust justification for why the sources used in the model to estimate the natural history of disease were selected.'* Gilead do not agree with the EAG's concerns regarding a lack of robust justification. The CS provided a detailed description of the approach taken: 'A

			pragmatic literature search was performed to identify natural history data in HDV. Given the data limitations and heterogeneity in study designs, it was deemed appropriate to calculate the natural history HDV progression based on publications comparing disease progression in HDV/HBV co-infected individuals versus treated HBV mono-infected patients. This approach was validated with clinical experts and health economists at a joint advisory board, 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.' During the clarification stage of this appraisal, further justification for the natural history sources was provided, for instance, a detailed justification for the use of the Fattovich (2003) (13) was provided as part of the response to clarification question B22.
Additional issue 3: Estimation of the probability of fibrosis progression from the F2-F4 states according to Romeo	Section 4.2.5.3.1., pages 80-82	Yes	The transition probability of progression from one of the F-stages to the next F-stage, e.g. progression from F2 to F3 was sourced from Fattovich (2003) and then increased 3-fold as per Da *et al*., 2019 (12,13). Fattovich (2003) reported a 20% probability of progression over a 5-year period (13). The EAR states that *'the EAG is unclear on how 20% over a 5-year period translated into a 5.3% probability and considers this should have translated into a 4.36% probability instead'*. We have double-checked this calculation and the EAG are correct, this should be 4.36%. We have updated this in the cost-effectiveness model. The EAG's base-case model uses estimates from Romeo *et al.*, (2009) to calculate fibrosis progression between F-states.

			Gilead are not aligned with the EAG's preference. As acknowledged by the EAG, *'the EAG caveats the Romeo estimates by the fact that they do not provide the probability of patients transitioning to the immediate next F-stage, but instead to the F4 stage'.* We therefore do not agree that the Romeo *et al.,* (2009) estimates are more appropriate than the base-case estimates, which are based on sources that specifically reported the risk of progression between F-stages. We acknowledge the EAG's statement that the Romeo *et al.*, (2009) estimates provide an alternative to assuming a constant progression in the F2 and in the F3 states, however we do not agree that there is sufficient basis to select these estimates over those applied in the company base-case.
Additional issue 4: Assuming that complete responders (CRs) have the same probability as partial responders (PRs), which is lower than the probability of non-responders (NRs), of developing HCC, instead of having a 0% probability of HCC	Section 4.2.5.3.1, Estimation of HRs to model disease progression for CRs in relation to NRs, pages 83-84	No	Whilst Gilead acknowledge there is a paucity of data around the probability of progressing to HCC in patients who achieve sustained virologic response, the EAG have not provided sufficient evidence to justify their preferred assumption therefore Gilead rejects the EAG's preferred assumption. Co-infected patients with HBV-HDV have an increased HCC risk compared with those patients with HBV mono-infection. HDV is a satellite virus, depending on the presence of HBV for its propagation; due to its nature and the scarcity of available data it is currently undetermined whether the higher risk of HCC in HBV-HDV coinfected individuals is the result of a cumulative effect of both viruses (HBV/HDV), the presence of cirrhosis or the oncogenic effect of HDV virus (14). In a retrospective, single centre study that was conducted in Taiwan to assess the role of HDV in development of HCC in CHB patients treated with analogues (NAs), 1349 CHB

			patients were consecutively enrolled and analysed for the period 2000-2018 (15). The study demonstrated that HDV viremia increases the risk of HCC and was in alignment with another Swedish retrospective study that showed that HDV RNA viremia is associated with higher risk for liver-related outcomes (15). Based on the available evidence, the scarcity on specific data, and the impact of HDV viremia in HCC risk, we believe that our assumptions in the model for complete, partial and non-responders are reasonable.
Additional issue 5: Using the [redacted] utility value to estimate the quality of life for NRs and PRs in the F-states, together with assuming a [redacted] utility value for CRs; and assuming that post-liver transplant (PLT) patients experience a [redacted] utility after transplant	Section 4.2.8., pages 90-92	No	In the company base-case, for the decompensated cirrhosis (DC), HCC, liver transplant (LT) and PLT health states, utilities were derived from a meta-analysis of chronic hepatitis B (CHB) utility values. The EAR states *'the EAG's clinical experts agreed that utility values for the CHB population can be considered a suitable proxy for the CHD population. Compared to previous TAs, the company's meta-analysis estimated higher utility values for the DC and the HCC health states, but much lower values for the LT and PLT states.'* The EAG argue that the PLT health state utility value applied in the company base-case (0.67) is too low in comparison with the F-stages utility values used by Gilead ([redacted]) or proposed by the EAG ([redacted]). The EAG's preferred base-case thus applies TA173-adjusted utility values to the PLT state. Gilead reject the EAG's preference for TA173-adjusted utility values for the PLT state. TA173 was published in 2009 and the utility values from this appraisal are therefore considered

			less relevant / out-of-date compared to the recent meta-analysis of HBV utilities that Gilead conducted and utilise in the CS. Furthermore, the EAG acknowledge that *'utility values from the company's meta-analysis may potentially be more robust as they are not reliant on a single study and include studies published after the release of TA153 and TA173 (over 13 years ago).'* We strongly agree with this assessment. We disagree with the EAG's statement that the PLT health state utility value (0.67) from the meta-analysis is too low. On the contrary, it could be argued that a utility value of [redacted] as proposed by the EAG, is considerably high for post liver-transplant patients, due to factors such as the burden of lifelong immunosuppression in most patients. A PLT patient would not be considered to have the same quality-of-life as a patient in one of the F-stages.
Additional issue 6: Adjusting utilities as per Ara and Brazier	Section 4.2.8, page 92	No	The Company explored the impact of age-related utility decrements in a scenario analysis.
Additional issue 7: Assuming that responders in the HCC health state carry on with bulevirtide treatment	Section 4.2.10	No	The aim of treatment with bulevirtide is to control CHD and stop progression of disease. Once patients have progressed to HCC, then the goal of treatment with bulevirtide is rendered obsolete, as treatment has failed to control the disease, regardless of whether they would be categorised as a responder or not. The SmPC states: "Treatment should be continued as long as associated with clinical benefit". The company base-case therefore assumes that treatment with bulevirtide continues until DCC, HCC, LT, PLT or death.

			In contrast to the SmPC, the EAG preferred base-case assumes that patients in the HCC state can continue treatment with bulevirtide. This assumption is based on feedback the EAG received from 2 clinical experts which provides conflicting interpretations to one another regarding the SmPC. The EAR states *'while one expert agreed that due to lack of trial evidence on treating patients with DC, treatment would be stopped upon decompensation; the other expert stated that treatment would be continued if patients developed DC or HCC.'* The SmPC states that "The use [of bulevirtide' in patients with decompensated liver disease is not recommended" because the safety and efficacy has not been established in patients with DCC. The EAG's scenario does not reflect the anticipated use of bulevirtide in the UK and is contrary to the SmPC and clinical advice which Gilead has received. The Company is of the opinion that is appropriate to assume that patients in the HCC health state discontinue treatment, as per the Company's base-case analysis.

3. Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	One-way impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Key issue 3: Uncertainty in the extrapolations beyond the observed trial data	Response rates were extrapolated based on aggregate data from MYR 301.	Response rates are extrapolated using individual patient data (IPD) from MYR 301, which is considered a more robust approach.	£231
Additional issue: Incorporation of further KOL feedback for monitoring resource use frequencies	Frequencies of HRU were informed by a sample of 3 KOLs.	Additional KOL feedback has been received from one KOL, increasing the sample of HRU responses to 4 KOLs. (See Resource Use table in CLINICAL sheet for pre- and post-estimates)	-£23
Additional issue – TP for progression from one F stage to the next F stage (Section 4.2.5.3.1)	The annual probability of progression from one F-stage to the next, e.g., from F2 to F3 was 15.07%.	The EAG highlighted that this was based on an erroneous calculation and this probability has now been updated to 12.53%. This is based on the 5-year progression rate observed in	+£436

		Fattovich et al., 2003 (13) multiplied by 3 as per the original model.	
Additional issue: Removing the F2 and F3 health state costs and including antiviral treatment costs for underlying HBV infection (Section 4.2.10).	Health state costs were included for the F2 and F3 states.	Health state costs are excluded for the F2 and F3 states.	-£792
Additional issue: Removing the F4 health state costs and including antiviral treatment costs for underlying HBV infection (Section 4.2.10)	Health state costs were included for the F4 state.	Health state costs are excluded for the F4 state.	-£292
Additional issue: Using the observed trial data to estimate transition probabilities in the economic model for bulevirtide and BSC (Section 4.2.5.2)	TPs were estimated using external literature.	The EAG's preferred base-case approach of using the observed trial data to estimate TPs is applied.	-£670

Note: The analyses do not reflect the impact of the revised PAS post-TE.

Table 5: Updated cost-effectiveness results (Company base-case post-Technical Engagement) – without severity modifier

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	8.31	[redacted]	-			
Bulevirtide	[redacted]	13.90	[redacted]	[redacted]	5.59	[redacted]	£33,134

Note: Includes revised PAS approved by NHSE&I and PASLU post-TE.

Table 6: Updated cost-effectiveness results (Company base-case post-Technical Engagement) – including severity modifier of 1.2

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	8.31	[redacted]	-			
Bulevirtide	[redacted]	13.90	[redacted]	[redacted]	5.59	[redacted]	£27,612

Note: Includes revised PAS approved by NHSE&I and PASLU post-TE.

References

1. National Institute for Health and Care Excellence. Hepatitis B (chronic): diagnosis and management | Guidance | NICE [Internet]. 2017 [cited 2021 Oct 26]. Available from: https://www.nice.org.uk/guidance/cg165/ifp/chapter/drug-treatment

2. Lampertico P, Agarwal K, Berg T, Buti M, Janssen HLA, Papatheodoridis G, et al. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol [Internet]. 2017 Aug 1 [cited 2021 Oct 26];67(2):370–98. Available from: https://pubmed.ncbi.nlm.nih.gov/28427875/

3. GSI - Data on file. MYR 301 Clinical Study Report. 2022;

4. Spaan M, Carey I, Bruce M, Shang D, Horner M, Dusheiko G, et al. Hepatitis delta genotype 5 is associated with favourable disease outcome and better response to treatment compared to genotype 1. J Hepatol [Internet]. 2020;72(6):1097–104. Available from: http://dx.doi.org/10.1016/j.jhep.2019.12.028

5. Cross TJS, Rizzi P, Horner M, Jolly A, Hussain MJ, Smith HM, et al. The increasing prevalence of hepatitis delta virus (HDV) infection in South London. J Med Virol [Internet]. 2008 Feb [cited 2021 Nov 16];80(2):277–82. Available from: https://pubmed.ncbi.nlm.nih.gov/18098143/

6. William Tong CY, Asher R, Toby M, Ngui SL, Tettmar K, Ijaz S, et al. A re-assessment of the epidemiology and patient characteristics of hepatitis D virus infection in inner city London. J Infect [Internet]. 2013 Jun [cited 2022 Aug 15];66(6):521–7. Available from: https://pubmed.ncbi.nlm.nih.gov/23466596/

7. El Bouzidi K, Elamin W, Kranzer K, Irish DN, Ferns B, Kennedy P, et al. Hepatitis delta virus testing, epidemiology and management: a multicentre cross-sectional study of patients in London. J Clin Virol [Internet]. 2015 May 1 [cited 2022 Aug 15];66:33–7. Available from: https://pubmed.ncbi.nlm.nih.gov/25866333/

8. Jackson C, Gunson RN, Bradley-Stewart A, Bennett S, Black H, Kennedy N, et al. Epidemiology and patient characteristics of hepatitis D virus infection in the West of Scotland 2011-2016. J Viral Hepat [Internet]. 2018 Nov 1 [cited 2022 Jun 20];25(11):1395–6. Available from: https://pubmed.ncbi.nlm.nih.gov/29851188/

9. Bigogno CM, Falahieh RR, Ho KMA, Jeffrey-Smith A, Jones M, Usai C, et al. The genetic landscape of hepatitis delta virus infection. Clin Med [Internet]. 2020 Mar 1 [cited 2022 Aug 23];20(Suppl 2):S101. Available from: https://pubmed.ncbi.nlm.nih.gov/32409407/

10. GSI - Data on file. Advisory Board Report. 2022.

11. National Institute for Health and Care Excellence (NICE). NICE Multiple Technology Appraisal ID1276 Selective internal radiation therapies for treating hepatocellular carcinoma. 2019;

12. Papatheodoridis G V., Chrysanthos N, Hadziyannis E, Cholongitas E, Manesis EK. Longitudinal changes in serum HBV DNA levels and predictors of progression during the natural course of HBeAg-negative chronic hepatitis B virus infection. J Viral Hepat. 2008;15(6):434–41.

13. Fattovich G. Natural history and prognosis of hepatitis B [Internet]. Vol. 23, Seminars in Liver Disease. Copyright © 2002 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA. Tel.: +1(212) 584-4662; 2003 [cited 2021 Oct 26]. p. 47–58. Available from: http://www.thieme-connect.com/products/ejournals/html/10.1055/s-2003-37590

14. Farci P, Niro GA, Zamboni F, Diaz G. Hepatitis d virus and hepatocellular carcinoma. Viruses. 2021;13(5).

15. Jang TY, Wei YJ, Liu TW, Yeh ML, Liu SF, Hsu CT, et al. Role of hepatitis D virus infection in development of hepatocellular carcinoma among chronic hepatitis B patients treated with nucleotide/nucleoside analogues. Sci Rep [Internet]. 2021;11(1):1–7. Available from: https://doi.org/10.1038/s41598-021-87679-w

Single Technology Appraisal: Bulevirtide for treating chronic hepatitis D [ID3732]

Technical engagement response form – Supplementary Appendix

Demographic data for people infected with hepatitis delta virus (HDV) in England is available from Public Health England (PHE). PHE routinely collect and report data on laboratories testing for hepatitis and HIV across all PHE Centre areas of England. This document summarises relevant data from the sentinel surveillance of blood borne virus testing in England for the last 10 years of available data (2011 to 2020). Table S1 presents key demographic data (age and sex) of individuals (n=897) testing positive for hepatitis D-specific total antibody (HDV TA) and/or a specific IgM antibody (anti-HDV IgM), a marker of HDV infection among those positive for hepatitis B. Testing was conducted from 01 Jan 2011 to 31 Dec 2020.

Table S1: Age and sex of the HDV positive individuals in England (2011 to 2020).

Source	Year of test	Sample size (n)	Median age (years)	Males
Public Health England (2021a)	2020	28	40	62%
Public Health England (2021b)	2019	33	36	59%
Public Health England (2020)	2018	168	36	53%
Public Health England (2018)	2017	129	36	56%
Public Health England (2017)	2016	90	34	54%
Public Health England (2016)	2015	100	37	63%
Public Health England (2015)	2014	97	36	54%
Public Health England (2014)	2013	97	36	56%
Public Health England (2013a)	2012	73	37	51%
Public Health England (2013b)	2011	82	37	55%
Average median value			**36**	55%
Weighted average			**36.2**	56%

References

1. Public Health England (2021a) Annual report from the sentinel surveillance of blood borne virus testing in England: data for January to December 2020. Health Protection Report, Vol. 15 (13). 28 July.

2. Public Health England (2021b) Annual report from the sentinel surveillance of blood borne virus testing in England 2019. Health Protection Report, Vol. 15 (2). 19 January.

3. Public Health England (2020) Annual Report from the sentinel surveillance of blood borne virus testing in England: data for January to December 2018. Health Protection Report, Vol. 14 (1). 14 January.

4. Public Health England (2018) Annual report from the sentinel surveillance study of blood borne virus testing in England: data for January to December 2017. Health Protection Report, Vol. 12 (36). 05 October.

5. Public Health England (2017) Annual report from the sentinel surveillance study of blood borne virus testing in England: data for January to December 2016. Health Protection Report, Vol. 11 (26). 28 July.

6. Public Health England (2016) Annual report from the sentinel surveillance study of blood borne virus testing in England: data for January to December 2015. Health Protection Report, Vol. 10 (24). 22 July.

7. Public Health England (2015) Annual report from the sentinel surveillance study of blood borne virus testing in England: data for January to December 2014. Health Protection Report, Vol. 9 (26). 24 July.

8. Public Health England (2014) Annual report from the sentinel surveillance study of blood borne virus testing in England: data for January to December 2013. Health Protection Report, Vol. 8 (29). 25 July.

9. Public Health England (2013a) Annual report from the sentinel surveillance study of blood borne virus testing in England: data for January to December 2012. Health Protection Report, Vol. 7 (30). 26 July.

10. Public Health England (2013b) Targeting Testing in England: Health Protection Services Sentinel Surveillance of Blood-Bourne Virus testing (SBV) in England, Annual review 2011. 30 January.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Bulevirtide for treating chronic hepatitis D [ID3732]

Technical engagement response form

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Technical engagement response form

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	NHS England – [redacted]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[redacted] I have a conflict of interest in that I have given lectures and consulted for Gilead but I am not involved in their delta virus program.

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Generalisability of trial population to the narrower population focused on by the company	Yes	Reviewing the information I think the advisory group has done an excellent job summarising the role of bulevirtide and hepatitis delta. Delta virus infection is uncommon but often aggressive leading to early cirrhosis and liver cancer. Current treatment has poor efficacy and many side effects. Bulevirtide therefore represents a significant step forward, but it is not an easy medication to administer and the committee is correct to adopt a sceptical tone to some of the companies claims. There is good evidence to show that the drug reduces viral activity and damage when given for 48 weeks and it is probable, although not yet proven, that this improvement will continue if therapy is extended. The short-term benefits are modest but likely to increase over time and I support the position adopted here that the drug should be restricted to those showing evidence of liver damage, who are most likely to derive early benefit from its use. I agree that there are clinical advantages with this drug but the duration of treatment, the magnitude of the long-term benefits and the cost-effectiveness of the drug are not yet clear. Given the redacted nature of the documents I will bow to the committee's decision on the cost effectiveness of treatment, but it seems likely that a price will be agreed that renders the drug cost-effective to the NHS for the clearly defined population considered here.

Key issue 2: Generalisability of trial population to UK patients	Yes/No	There are two issues for NHSE to consider. 1) Mode of distribution/administration. Patients with delta virus who may be eligible for this treatment require a careful pre-treatment assessment by an experienced clinician and considerable support during therapy, which is not trivial to administer. Assessing the degree of fibrosis is not trivial as the conventional tests (e.g. fibroscan) may be artificially raised by the inflammatory reaction often associated with this infection and the decision on 'tolerance' to interferon requires fine judgement. We have a network of experienced viral hepatitis treatment providers in the hepatitis C ODNs and, given the likely reduction in activity over the next few years as hepatitis C is eliminated, there is capacity in the networks to provide a high quality, equitable national service that ensures that all patients with delta virus can access appropriate care. I strongly recommend that treatment is restricted to experienced centres and using the hepatitis C infrastructure would be a cost-effective way to do so.
Key issue 3: Uncertainty in the extrapolations beyond the observed trial data	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 4: Modelling of HCC	Yes/No	Treatment duration. The data supports 48 weeks therapy and emerging data suggests that prolonging therapy will be beneficial, although this does not yet reach the stage of formal proof. Hence in patients who are responding, or potentially responding, it is unclear how to proceed after 48 weeks. It seems highly unlikely that physicians or patients will agree to discontinue a treatment when no other options are available and I suspect that once a patient is started on bulevirtide they will remain on it for many years. It is not known whether therapy for several years will lead to viral clearance and safe drug withdrawal but given that therapy for decades in HBV rarely leads to viral clearance it seems likely that therapy for many years will be required to achieve a 'cure' from delta virus. NHSE will need to develop a response to the inevitable question after 48 weeks therapy

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

NICE National Institute for Health and Care Excellence

Summary of changes to the company's cost-effectiveness estimate(s)

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Table 4 Changes to the company's cost-effectiveness estimate

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Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
PLEASE DESCRIBE HERE

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Bulevirtide for treating chronic hepatitis D [ID3732]

Technical engagement response form

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NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	British Association for Sexual Health and HIV
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Generalisability of trial population to the narrower population focused on by the company	No	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 2: Generalisability of trial population to UK patients	No	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 3: Uncertainty in the extrapolations beyond the observed trial data	No	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 4: Modelling of HCC	No	Please provide your response to this key issue, including any new evidence, data or analyses

Additional issues

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Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Increased risk of Hepatocellular carcinoma for people living with HIV-HBV-HDV co-infection	**4.2.6.1**	**Yes**	**In addition to Beguelin et al, Kamal et al states *"A six-fold significant increased risk of HCC was noted among HIV/HBV/HDV triple-infected, compared to HIV/HBV co-infected patients"* from a systematic review and metanalysis of twelve cohort studies.** **https://doi.org/10.1111/jvh.13577** **People with HIV should not be excluded from access to the new therapy, and indeed cost-effectiveness may be greater in people with HIV/HBV/HDV.**
Additional issue 2:	Please indicate the section(s) of the EAR that discuss this issue	No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

NICE National Institute for Health and Care Excellence

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Key issues for engagement

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Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Generalisability of trial population to the narrower population focused on by the company	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 2: Generalisability of trial population to UK patients	Yes/No	I am the lead investigator of a study (being funded by Gilead) of the epidemiology of HDV infection in the UK. The study is currently collecting data from all (n = 10) virology laboratories in the UK that undertake any form of HDV testing. Those data are being de-duplicated so that we can produce a definitive list of all patients diagnosed as either anti-HDV and/or HDV RNA positive in the UK in the last 10 years. We are aiming to have this analysis complete by mid-September, and I would be happy to share the results with NICE if you would like to see them. At this stage, we will only have access to demographic information, but I believe this will include date of birth, so this should be able to answer your question about the age of patients. We are also creating a disease register for HDV-infected patients, to be held at UKHSA. Having identified all diagnosed patients as above, we will be asking clinicians to enter data on the liver disease (and treatment) status of those

		patients. Data collection forms will be distributed in early September. We hope to have most of the data returned by end 2022. As we hope to publish all of the above data in due course, the data would be submitted as academic in confidence
Key issue 3: Uncertainty in the extrapolations beyond the observed trial data	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 4: Modelling of HCC	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses

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Sensitivity analyses around revised base case
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Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **2 September 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Technical engagement response form

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Gilead Sciences Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None.

Introduction

Gilead would like to thank the NICE technical team for reviewing the company submission for bulevirtide for the treatment of hepatitis delta, preparing the technical report, and for providing us with the opportunity to engage in the technical engagement process.

Our response is split into four separate parts:

1) Company response to the four key issues identified in the EAR
2) Company response to the additional issues raised by the EAG
3) Details of the revised company base case in response to the EAR
4) Additional supportive evidence, provided as a technical appendix

Gilead acknowledge the uncertainty in the extrapolations of the MYR 301 efficacy data that were highlighted within the EAR. To address the uncertainty associated with the original extrapolations, we have explored alternative methods of extrapolating the MYR 301 efficacy data. This is discussed in detail in the response to key issue 3 and has been included within this response document as additional supportive evidence. Further details regarding the extrapolation methodology are submitted as part of a supplementary technical appendix.

1. Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response	EAG response
Key issue 1: Generalisability of trial population to the narrower population focused on by the company	Yes	**The overall MYR 301 trial population is likely to be IFN-based therapy experienced, intolerant, or contraindicated and is therefore reflective of the position adopted in the CS** The Evidence Assessment Group (EAG) highlighted that it was unclear as to what proportion of patients enrolled in the pivotal MYR 301 study were contraindicated or ineligible for treatment with interferon-based therapy (hereafter referred to as IFN-based therapy), and therefore queried the generalisability of the trial population with the narrower population specified in the decision problem. In the full trial population of the MYR 301 clinical study, 56.0% of subjects had received prior treatment with IFN-based therapy. Treatment guidelines for the management of hepatitis B virus (HBV)/hepatitis delta virus (HDV) co-infection recommend treatment with peginterferon alfa-2a (PEG-IFN), and it is expected to be offered to almost all chronic hepatitis delta (CHD) patients with compensated liver disease (1,2). As such, it is considered likely that patients who had not received prior IFN-based therapy at baseline were	Please refer to the EAG's response to the company's technical engagement comments.

		not offered this treatment as they were either contraindicated or unlikely to tolerate treatment. These patients would therefore fall within the proposed population in the company submission (CS). This is supported by the EAG's clinical experts, who highlighted that '*the limitations of PEG-IFN treatment mean that a substantial portion of patients with CHD, compensated liver disease and significant fibrosis are not offered treatment with PEG-IFN as they are either contraindicated or are unlikely to tolerate treatment.'* On this basis, whilst Gilead acknowledge that in the absence of recorded data the percentage of patients who were not offered IFN-based therapy due to intolerance or contraindication is not defined, we propose that this is likely to be almost all patients who had not received prior IFN-based therapy at baseline. **Combined response is the key driver of the model** The EAG hypothesise that it may *potentially* be easier for patients with a lower METAVIR fibrosis stage (F0 or F1) to achieve biochemical response, which if true could lead to an overestimate of efficacy in the bulevirtide 2 mg treatment arm versus best supportive care (BSC) in the full trial population. However, the model is driven by the achievement of a combined response, which requires the fulfilment of a biochemical response and a virologic response. A virologic response was defined as undetectable (< limit of detection [LoD]) HDV ribonucleic acid (RNA) or decrease by ≥2-$\log_{10}$ IU/mL from baseline at Week 48. It is also worth noting that in contrast to alanine aminotransferase (ALT) normalisation, the percentage of patients achieving a virologic response in the bulevirtide 2 mg treatment arm was greater in the subgroup of patients with cirrhosis ([redacted] of 23 patients) compared to the non-cirrhotic subgroup ([redacted] of 26 patients) (3). **The cirrhotic subgroup includes significant amounts of missing data**	

		The EAG recommended that a scenario analysis focusing on the cirrhotic subgroup of patients in MYR 301 was included within the model. In lieu of response data by METAVIR fibrosis stage, the EAG considered this scenario to be the best proxy for estimating the contribution of participants with METAVIR stages F0 or F1 to the overall study results. Whilst Gilead acknowledges a slight imbalance between treatment arms with regards to proportion classified as METAVIR fibrosis stages F0 or F1 in the overall population, constituting [redacted] of patients ([redacted] of 49 patients) in the bulevirtide 2 mg treatment arm and [redacted] of patients ([redacted] of 51 patients) in the delayed treatment arm, we would challenge the EAG's preference for the cirrhotic subgroup as a more appropriate proxy. In the pivotal MYR 301 clinical study, liver biopsies were not a requirement for trial inclusion, and the EAG's clinical experts note in Section 2.3.1 of the technical report that liver biopsy is always discussed with patients likely to have advanced liver disease, but often not favoured by patients due to the invasive nature of the procedure. As presented in Table 1.1, for the cirrhotic subgroup data on fibrosis stage was only available for [redacted] of patients ([redacted] of 24 patients) in the delayed treatment arm and [redacted] of patients ([redacted] of 23 patients) in the bulevirtide 2 mg treatment arm. Furthermore, whilst the numbers classified as METAVIR fibrosis stage F0 or F1 are balanced between arms, the proportion of these amongst those with data available are imbalanced. Of those with biopsy performed at baseline, [redacted] of patients ([redacted] patients) in the delayed treatment arm, and [redacted] of patients ([redacted] patients) in the bulevirtide 2 mg arm were classified as METAVIR fibrosis stages F0 or F1. With the additional confounder of missing data for [redacted] of the cirrhotic subgroup as described in the previous paragraph, Gilead do not consider this proxy to be a preferable approach to using the full trial population. **Table 1.1: METAVIR fibrosis scores at baseline of MYR 301 cirrhotic participants**	

Arm	METAVIR fibrosis score at baseline					
	F0	F1	F2	F3	F4	Missing
Cirrhotic participants						
Delayed Treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bulevirtide 2 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

As requested by the EAG, an exploratory scenario analysis using the cirrhotic subgroup response data applied to the F2-F4 population was run in the model. Efficacy data for the cirrhotic subgroup were available for up to Week 48 of MYR 301 and thus virological and composite response was taken from the clinical study report (CSR) for the cirrhotic and non-cirrhotic subgroup. The proportion of responders in the cirrhotic and non-cirrhotic subgroups was weighted based on the proportion of non-cirrhotic to non-cirrhotic patients at baseline within the model. For the extrapolated timepoints within the model (72 and 96 weeks), we modelled response for the cirrhotic/non-cirrhotic subgroup by assuming the same relative increase in response from extrapolating as observed in the overall population. The results for this scenario are presented in Table 1.2 below, compared with our updated company base case (see Table 4 and Issue 2).

Table 1.2: Scenario analysis results using cirrhotic subgroup response rates from MYR 301

Interventions	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	Base-case ICER[1]
Results without severity modifier					
BSC	-	-	-	-	-
Bulevirtide	[redacted]	5.28	[redacted]	£40,657	£39,691
Results including severity modifier of 1.2					
BSC	-	-	-	-	-
Bulevirtide	[redacted]	5.28	[redacted]	£33,881	£33,076

		Note 1: Updated company base case, see Table 4 and Issue 3. This exploratory scenario analysis shows that removing the perceived imbalance between treatment arms in terms of METAVIR fibrosis stage, by assessing the treatment effect of bulevirtide based on the balanced cirrhotic subgroup, has only a marginal impact on the ICER.	
Key issue 2: Generalisability of trial population to UK patients	Yes	**Baseline characteristics from external UK-specific literature sources are more appropriate for the economic model** Although the pivotal MYR 301 clinical study did not enrol any patients from the UK, it represents the best source of clinical efficacy and safety data regarding the treatment of CHD with bulevirtide compared to best supportive care. The pivotal Phase 3 MYR 301 study enrolled 150 patients across 16 study sites located across Russia (7 sites), Germany (5 sites), Italy (3 sites) and Sweden (1 site). The average age of participants in the full trial population was 41.8 years, and 57.3% were male. Almost half of the participants (47.3%) had cirrhosis at the time of enrolment based on investigator assessment. In the absence of UK clinical trial sites in the pivotal study, baseline characteristics from Spaan *et al*., (2020), who carried out a long-term retrospective analysis of 107 CHD patients in the UK population, were used to inform the economic model. Compared to MYR 301, a lower mean age of 35.1 years was observed in the actively replicating HDV patient population, comprising 46 patients in total. Furthermore, 58.7% of these participants were male and 50.0% of patients with actively replicating HDV had cirrhosis (4). The EAG's clinical experts consider that '*while the baseline characteristics included in the company's model were representative of the UK population, the baseline characteristics in the trial were not clinically implausible*'. Gilead notes that the EAG's clinical experts are aligned with the use of baseline characteristics from Spaan *et al*., (2020) in the economic model. Whilst we	Given how sensitive the cumulative ICERs are to relatively small variations in baseline age and cirrhotic distribution in the model (see Section 6.2 of the EAR), the EAG considers that the additional data provided by the company highlights the uncertainty around these parameters. Given the response to TE from one clinical expert who is lead investigator of a study of the epidemiology of HDV infection in the UK (funded by Gilead), advising that data from 10 virology laboratories in the UK in the last 10 years will be completed by mid-September, the EAG recommends that the company includes a scenario analysis using these data before the ACM.

also acknowledge the experts considered that the baseline characteristics from MYR 301 are 'not clinically implausible', this appears to be a relatively weak endorsement compared to the UK-specific study conducted by Spaan *et al*., (2020). UK clinical experts have advised Gilead that it is appropriate to utilise the Spaan *et al.,* (2020) study for baseline demographic data. Furthermore, the EAG have not provided any evidence from their clinical experts to say that the Spaan *et al.,* (2020) study is inappropriate.

As recommended by the EAG, Gilead have presented available data from the literature regarding the typically presenting age and cirrhotic distribution of CHD patients in the UK in Table 2.1 below. The baseline age and proportion of cirrhotic patients published by Spaan *et al*., (2020) is supported by additional external literature sources.

Table 2.1: External literature sources for baseline age and cirrhotic status of CHD patients in the UK

Reference	Sample size (n)	Age (years)	Cirrhotic (%)
Cross *et al*., (2008) (5)	82	Median: 36.0	26.8
Tong *et al*., (2013) (6)	33	Mean: 35.4	59.1
El Bouzidi *et al*., (2015) (7)	55	Median: 40.0	49.0
Jackson *et al*., (2018) (8)	23	Mean: 36.0	NR
Spaan *et al*., (2020) (4)	46	Mean: 35.1	50.0
Bigogno *et al*., (2020) (9)	16	Median: 37.0	NR

Abbreviations: NR: not reported.

Whilst not all publications report the cirrhotic status of patients, there appears to be a consensus of approximately 50.0%, based on data from Tong *et al.,* (2013), El Bouzidi e*t al*., (2015), and Spaan *et al*., (2020). A clinical expert attending a Gilead advisory board also highlighted that the proportion of patients with cirrhosis in the MYR 301 study population (47.3%) was lower than what they may expect for the UK CHD population

		(10). In conclusion, Gilead strongly stands by its approach of using baseline demographics from Spaan *et al*., (2020) in the economic model and believes that the use of this data source is supported by the EAG's clinical experts.	
Key issue 3: Uncertainty in the extrapolations beyond the observed trial data	Yes	**Extrapolation of response rates using MYR 301 individual patient data (IPD)** We acknowledge the uncertainty in the extrapolations that were highlighted within the EAR. During technical engagement, Gilead have explored alternative methods of extrapolating the MYR 301 trial data. In the original submission, response rates were extrapolated based on aggregate data from MYR 301. We have therefore extrapolated the trial data using IPD which may be considered a more robust approach. IPD was used for the long-term extrapolation of 5 endpoints: - ALT (biochemical) response - HDV RNA decrease - HDV RNA undetectability - Virologic response - Composite response Based on the IPD, extrapolation was performed using nonlinear least squares (NLSE) regression, with a binomial link function. Compared to the EMAX approach, fitting the data to a parametric function using NLSE estimation is more flexible, since patients can be classified as responders or non-responders at each specific time-point, based on the distributional form of the patients at that time-point. An assessment of the suitability of each fitted model to the observed and predicted data was undertaking using several methods including visual inspection, statistical tests of relative fit, and by considering the clinical plausibility of the extrapolations. Internal validation was assessed by using	The EAG agrees that the company's updated approach for extrapolating data provides more plausible curves. However, the EAG notes that the key concerns raised in issue 3 of the EAR have not been addressed by the company. These are discussed in the EAG's response to the company's technical engagement comments.

		Akaike Information Criterion (AIC) to assess the relative fit of the alternative parametric models including logistic, log-logistic, and Weibull. The log-logistic model provided a clinically plausible estimate and was considered the best parametric fit to the IPD. Other validation methods, such as cross-validation, were deemed inappropriate given the small sample size. Overall, the new extrapolation approach provides a more conservative fit to the data, compared to the EMAX approach, whilst still predicting a sustained and high response up to the extrapolated period of 76 to 92 weeks. For example, for the proportion of patients on bulevirtide 2mg, over the period of 4 to 48 weeks IPD: • The proportion of predicted combined and virologic responders using the log-logistic model using NLSE provides a much closer fit to the observed IPD than the EMAX model. Specifically, this is evident in Weeks 24 to 40, where the EMAX under-predicted the proportion of responders and then, at 48 weeks, over-predicted the results by an average of roughly 13% for both combined and virologic responders. Similar trends are observed in the EMAX model for the endpoint of HDV RNA undetectable. • In comparison, the log-logistic model using NLSE notably provides a much closer fit to the observed IPD whilst still predicting a high and sustained response across the 5 endpoints. In addition, for the proportion of subjects on delayed treatment: • The EMAX model under-predicts the proportion of patients showing combined response versus the observed data. In comparison, the log-logistic model using NLSE, for example, provides a much closer fit to the model all endpoints. Therefore, given these trends as well as the improved AIC scores and visual fits, the log-logistic model reduces extrapolation uncertainties. It is important to note that the primary limitation of using the NLSE method is that the estimated proportion of responders may become greater than 100%, over a	

longer period of follow-up. Nevertheless, this limitation does not impact the predictions over a relatively short follow-up, such as the 72 or 96 weeks period used for this extrapolation, however it is an important consideration when implementing the IPD extrapolations into the cost-effectiveness analysis.

Incorporation of new extrapolations into cost-effectiveness model

The new set of extrapolations, based on MYR 301 IPD were incorporated into the cost-effectiveness model and are applied in the updated, post technical engagement company base-case which results in an ICER of £39,691. For comparison, the new company base case excluding the new extrapolations is presented below:

Table 3.1: Cost-effectiveness results, updated base-case with new method of extrapolating MYR 301 data

Interventions	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER excluding new extrapolation (£/QALY)	ICER[1] (£/QALY)
Results without severity modifier					
BSC	-				
Bulevirtide	[redacted]	5.46	[redacted]	£38,852	£39,691
Results including severity modifier of 1.2					
BSC	-				
Bulevirtide	[redacted]	5.46	[redacted]	£32,376	£33,076

Note 1: Updated company base case, see Table 4 for other changes.

It is noteworthy that as per the original submitted base-case, extrapolated data are only used at Week 72 within the model. 96-week data from MYR

		301 is expected in [redacted], which will aid in addressing the uncertainty in response rates beyond 48 weeks in the model.	
Key issue 4: Modelling of HCC	Yes	**Clinician validation** As recommended by the EAG, Gilead sought to validate the assumptions around the way hepatocellular carcinoma (HCC) was modelled in the submitted cost-effectiveness model. A questionnaire was sent out via email to clinical experts based in the UK. The assumptions regarding the modelling of HCC, in particular the possible health state transitions from this state were outlined, followed by a set of questions asking the experts to state whether the model's assumptions were realistic, whether cure was a clinical reality for CHD patients and if yes, the proportion of patients that they would estimate to be cured or progression-free from HCC. 2 leading clinical experts in the UK provided advice. Of note, one of the clinical experts stated that the proportion of CHD patients eligible for procedures such as resection or ablations (which the EAR states can be curative in HCC) is very low, approximately 10% to 20%, as most CHD patients have significant portal hypertension. With regards to proportions achieving cure, both KOLs stated that this would be a very small number of patients, approximately 30%. **Scenario including cure for HCC patients** As recommended by the EAG, we have updated the cost-effectiveness model to include a scenario where a proportion of HCC patients can transition to a progression-free state of the disease. This has been implemented by including a cell in the settings sheet, specifying the proportion of HCC patients who are assumed to be cured. The proportion cured is assumed to have both a higher utility value and lower mortality rate than uncured patients, with overall utility and mortality rates for HCC patients calculated as a weighted average of cured and uncured values.	Please refer to the EAG's response to the company's technical engagement comments.

There is a scarcity of published data on the proportions of cure in HCC patients who had CHD. In line with the feedback received from clinical experts, we assumed a proportion of 30% cure for this scenario and implemented this by reducing excess mortality from HCC by 30% and adjusting the health state utilities for cured HCC patients as follows:

- For those patients who remain uncured, the original health state utility of 0.52 is applied, whilst for the proportion who are cured, a utility of 0.70 is applied. The 0.70 utility value was sourced from the PFS health state utility value that was applied for the standard of care arm in NICE TA688 (Selective internal radiation therapies (SIRT) for treating HCC) (11).

As can be seen in the table below, this scenario analysis had a marginal impact on the ICER; the cure assumption did not increase the ICER substantially compared to the revised, post-technical engagement company base-case ICER (£39,913 vs. £39,691 per QALY).

Table 4.1: Cost-effectiveness analysis results for scenario where 30% of HCC patients are assumed cured

Interventions	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER[1] (£/QALY)	Base-case ICER[1]	Pre-Technical Engagement ICER (£/QALY)
Results without severity modifier						
BSC				-	-	£40,189
Bulevirtide	[redacted]	5.50	[redacted]	£39,913	£39,691	
Results including severity modifier of 1.2						
BSC				-	-	
Bulevirtide	[redacted]	5.50	[redacted]	£33,261	£33,076	

Note 1: Updated company base case, see Table 4 and Issue 3.

2. Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response	EAG response
Additional issue 1: Assuming that 48 weeks is the maximum timeframe for assessing final response to treatment, and treatment effectiveness is not extrapolated e.g., assume response rates do	Section 4.2.4.1, pages 67-68	No	In the company base-case, observed MYR 301 response rates inform modelled response rates at Weeks 24 and 48. As stated in the original CS, although the available follow-up data from MYR 301 are limited to 48 weeks, analysis of the individual patient data (IPD) indicates that response rates were still increasing at that timepoint. A clear trend can be observed which shows that virologic and combined response rates are increasing over time. Therefore, the proportion of complete responders among those remaining on treatment past 48 weeks is expected to	Although the EAG agrees that the company's updated extrapolations provide more plausible results, there are key issues related to treatment discontinuation in the trial that need clarifying with more mature data (i.e., the 96-week data). Therefore, the EAG's preference is still to only use observed data in the model for the 48-week period available until the more mature data are available.

not improve beyond Week 48.			increase. The response rates for the 2mg bulevirtide and delayed treatment arms of MYR 301 up until week 48 were therefore extrapolated to estimate treatment response at Weeks 72 and 96. The EAG's preferred base-case assumes that 48 weeks is the maximum timeframe for assessing final response to treatment with bulevirtide: efficacy data from MYR 301 are not extrapolated, that is, it is assumed that response rates do not improve beyond Week 48. The company provided this as a scenario in the original CS (see Section B.3.11, pages 157-159). Gilead disagree with the EAG's statement that limiting the timeframe for assessing response to 48 weeks is a more robust method compared to the extrapolation of efficacy data. A clear trend of improving response rates can be observed in the data. Furthermore, extrapolations are only applied in the model until Week 72, which is a conservative assumption and is not clinically implausible. Functionality is provided in the model to explore the impact on the ICER of assessing response (partial and complete) at week 96.	

			As stated in the original CS, the Week 48 assessment can be considered an early assessment of efficacy that evaluates achievement of a virologic response (HDV-RNA undetectability or ≥2-log_{10} decline) while the Week 72 assessment can be considered a definitive assessment of both virologic and biochemical response (MYR 301 primary endpoint; composite response of HDV-RNA undetectability or 2-log_{10} decline and ALT normalisation at Week 48). Having these two continuation rules allows sufficient time for patients to achieve a clinical response (given that response rates were still increasing at Week 48 in MYR 301). In other words, at Week 48 the model evaluates both virologic and biochemical response as per the MYR 301 primary endpoint. Those who fail to show virologic response are classified as non-responders and discontinue bulevirtide. However, the model applies a definitive assessment of the composite endpoint at Week 72 for patients that had achieved the virologic response to allow sufficient time for patients to achieve ALT normalisation and therefore, clinical response as defined by the composite endpoint (virologic and biochemical response) as in MYR 301.	

			The EAG's clinical expert feedback that 'response (or lack thereof) to treatment is assessed well before 48 weeks, at 3 or 6 months' is not aligned with the feedback Gilead received from. Clinicians attending an advisory board stated that they preferred 48 weeks over 24 weeks as a timepoint for the stopping rule within the model. It was widely agreed that 24 weeks was not the optimal time to take a view of the efficacy of bulevirtide. Clinicians were aligned on a stopping rule at 48 weeks if patients were not responding with bulevirtide. A timepoint of 3 to 6 may also be considered too premature to assess response given the NICE clinical guideline for chronic hepatis B which states that clinicians should *'Consider stopping peginterferon alfa-2a if there is no decrease in HDV RNA after 6 months to 1 year of treatment. Otherwise, continue treatment and re-evaluate treatment response annually'.* Additionally, the EAG's opinion is in contrast to the SmPC which states: 'treatment should be continued as long as associated with clinical benefit'.	
Additional issue 2: Estimation of the probability of hepatocellular carcinoma (HCC)	Table 25, Section 4.2.5.3.1., page 78	No	In the cost-effectiveness model, the natural history of CHD was modelled using estimates sourced from published literature. The EAR states that *'the EAG is concerned that the company did not*	The EAG maintains its position as discussed in the EAR, Section 4.2.5.3.1.

from the F2-F4 states according to Romeo and Kushner			*provide a robust justification for why the sources used in the model to estimate the natural history of disease were selected.'* Gilead do not agree with the EAG's concerns regarding a lack of robust justification. The CS provided a detailed description of the approach taken: 'A pragmatic literature search was performed to identify natural history data in HDV. Given the data limitations and heterogeneity in study designs, it was deemed appropriate to calculate the natural history HDV progression based on publications comparing disease progression in HDV/HBV co-infected individuals versus treated HBV mono-infected patients. This approach was validated with clinical experts and health economists at a joint advisory board, 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.' During the clarification stage of this appraisal, further justification for the natural history sources was provided, for instance, a detailed justification for the use of the Fattovich (2003) (13) was	

			provided as part of the response to clarification question B22.	
Additional issue 3: Estimation of the probability of fibrosis progression from the F2-F4 states according to Romeo	Section 4.2.5.3.1., pages 80-82	Yes	The transition probability of progression from one of the F-stages to the next F-stage, e.g. progression from F2 to F3 was sourced from Fattovich (2003) and then increased 3-fold as per Da *et al*., 2019 (12,13). Fattovich (2003) reported a 20% probability of progression over a 5-year period (13). The EAR states that *'the EAG is unclear on how 20% over a 5-year period translated into a 5.3% probability and considers this should have translated into a 4.36% probability instead*'. We have double-checked this calculation and the EAG are correct, this should be 4.36%. We have updated this in the cost-effectiveness model. The EAG's base-case model uses estimates from Romeo *et al.*, (2009) to calculate fibrosis progression between F-states. Gilead are not aligned with the EAG's preference. As acknowledged by the EAG, *'the EAG caveats the Romeo estimates by the fact that they do not provide the probability of patients transitioning to the immediate next F-stage, but instead to the F4 stage'.* We therefore do not agree that the Romeo *et al.,* (2009) estimates are more appropriate	The EAG maintains its position as discussed in the EAR, Section 4.2.5.3.1.

			than the base-case estimates, which are based on sources that specifically reported the risk of progression between F-stages. We acknowledge the EAG's statement that the Romeo *et al.*, (2009) estimates provide an alternative to assuming a constant progression in the F2 and in the F3 states, however we do not agree that there is sufficient basis to select these estimates over those applied in the company base-case.	
Additional issue 4: Assuming that complete responders (CRs) have the same probability as partial responders (PRs), which is lower than the probability of non-responders (NRs), of developing HCC, instead of having a 0% probability of HCC	Section 4.2.5.3.1, Estimation of HRs to model disease progression for CRs in relation to NRs, pages 83-84	No	Whilst Gilead acknowledge there is a paucity of data around the probability of progressing to HCC in patients who achieve sustained virologic response, the EAG have not provided sufficient evidence to justify their preferred assumption therefore Gilead rejects the EAG's preferred assumption. Co-infected patients with HBV-HDV have an increased HCC risk compared with those patients with HBV mono-infection. HDV is a satellite virus, depending on the presence of HBV for its propagation; due to its nature and the scarcity of available data it is currently undetermined whether the higher risk of HCC in HBV-HDV coinfected individuals is the result of a	The EAG maintains its position as discussed in the EAR, Section 4.2.5.3.1

			cumulative effect of both viruses (HBV/HDV), the presence of cirrhosis or the oncogenic effect of HDV virus (14). In a retrospective, single centre study that was conducted in Taiwan to assess the role of HDV in development of HCC in CHB patients treated with analogues (NAs), 1349 CHB patients were consecutively enrolled and analysed for the period 2000-2018 (15). The study demonstrated that HDV viremia increases the risk of HCC and was in alignment with another Swedish retrospective study that showed that HDV RNA viremia is associated with higher risk for liver-related outcomes (15). Based on the available evidence, the scarcity on specific data, and the impact of HDV viremia in HCC risk, we believe that our assumptions in the model for complete, partial and non-responders are reasonable.	
Additional issue 5: Using the [redacted] utility value to estimate the quality of life for NRs and PRs in the F-states, together with	Section 4.2.8., pages 90-92	No	In the company base-case, for the decompensated cirrhosis (DC), HCC, liver transplant (LT) and PLT health states, utilities were derived from a meta-analysis of chronic hepatitis B (CHB) utility values. The EAR states *'the EAG's clinical experts agreed that utility values for the CHB population can be considered a*	The EAG maintains its view that the utility value for the PLT health used in the company's base case is too low in comparison with the F-stages utility values used by the company, especially as this is the permanent health state for patients whose liver transplant was successful.

assuming a [redacted] utility value for CRs; and assuming that post-liver transplant (PLT) patients experience a [redacted] utility after transplant			*suitable proxy for the CHD population. Compared to previous TAs, the company's meta-analysis estimated higher utility values for the DC and the HCC health states, but much lower values for the LT and PLT states.'* The EAG argue that the PLT health state utility value applied in the company base-case (0.67) is too low in comparison with the F-stages utility values used by Gilead ([redacted]) or proposed by the EAG ([redacted]). The EAG's preferred base-case thus applies TA173-adjusted utility values to the PLT state. Gilead reject the EAG's preference for TA173-adjusted utility values for the PLT state. TA173 was published in 2009 and the utility values from this appraisal are therefore considered less relevant / out-of-date compared to the recent meta-analysis of HBV utilities that Gilead conducted and utilise in the CS. Furthermore, the EAG acknowledge that *'utility values from the company's meta-analysis may potentially be more robust as they are not reliant on a single study and include studies published after the release of TA153 and TA173 (over 13*	As such, the EAG considers that the two scenarios ran by the EAG are relevant – one where patients in the PLT state were assumed to return to their original utility value before they progressed from the F-stages; and another where the relative difference from TA173 between the CC state the DC, HCC, LT, and PLT was applied to the EAG's preferred baseline utility value of [redacted] from MYR 301. Crucially, the EAG notes that using different utilities for the LT state had a small impact on the ICER (see Section 6.3 of the EAR).

			years ago).' We strongly agree with this assessment. We disagree with the EAG's statement that the PLT health state utility value (0.67) from the meta-analysis is too low. On the contrary, it could be argued that a utility value of [redacted] as proposed by the EAG, is considerably high for post liver-transplant patients, due to factors such as the burden of lifelong immunosuppression in most patients. A PLT patient would not be considered to have the same quality-of-life as a patient in one of the F-stages.	
Additional issue 6: Adjusting utilities as per Ara and Brazier	Section 4.2.8, page 92	No	The Company explored the impact of age-related utility decrements in a scenario analysis.	The EAG maintains its position as discussed in the EAR, Section 4.2.8.
Additional issue 7: Assuming that responders in the HCC health state carry on with bulevirtide treatment	Section 4.2.10	No	The aim of treatment with bulevirtide is to control CHD and stop progression of disease. Once patients have progressed to HCC, then the goal of treatment with bulevirtide is rendered obsolete, as treatment has failed to control the disease, regardless of whether they would be categorised as a responder or not. The SmPC states: "Treatment should be continued as long as associated with clinical benefit". The company base-case therefore assumes that treatment with	The EAG notes that while the SmPC states that treatment should be discontinued upon decompensation, it does not include a stopping rule explicitly for HCC. Given the EAG's expert opinion that treatment with bulevirtide would continue in patients with HCC, the EAG still considers this to be a relevant scenario analysis. Nonetheless, the EAG acknowledges that carrying on treatment for HCC patients might be less common than stopping

			bulevirtide continues until DCC, HCC, LT, PLT or death. In contrast to the SmPC, the EAG preferred base-case assumes that patients in the HCC state can continue treatment with bulevirtide. This assumption is based on feedback the EAG received from 2 clinical experts which provides conflicting interpretations to one another regarding the SmPC. The EAR states *'while one expert agreed that due to lack of trial evidence on treating patients with DC, treatment would be stopped upon decompensation; the other expert stated that treatment would be continued if patients developed DC or HCC.'* The SmPC states that "The use [of bulevirtide' in patients with decompensated liver disease is not recommended" because the safety and efficacy has not been established in patients with DCC. The EAG's scenario does not reflect the anticipated use of bulevirtide in the UK and is contrary to the SmPC and clinical advice which Gilead has received. The Company is of the opinion that is appropriate to assume that patients in the HCC health state discontinue treatment, as per the Company's base-case analysis.	treatment, therefore, the EAG removed this assumption from its base case ICER.

3. Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	One-way impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Key issue 3: Uncertainty in the extrapolations beyond the observed trial data	Response rates were extrapolated based on aggregate data from MYR 301.	Response rates are extrapolated using individual patient data (IPD) from MYR 301, which is considered a more robust approach.	£231
Additional issue: Incorporation of further KOL feedback for monitoring resource use frequencies	Frequencies of HRU were informed by a sample of 3 KOLs.	Additional KOL feedback has been received from one KOL, increasing the sample of HRU responses to 4 KOLs. (See Resource Use table in CLINICAL sheet for pre- and post-estimates)	-£23
Additional issue – TP for progression from one F stage to the next F stage (Section 4.2.5.3.1)	The annual probability of progression from one F-stage to the next, e.g., from F2 to F3 was 15.07%.	The EAG highlighted that this was based on an erroneous calculation and this probability has now been updated to 12.53%. This is based on the 5-year progression rate observed in	+£436

		Fattovich et al., 2003 (13) multiplied by 3 as per the original model.	
Additional issue: Removing the F2 and F3 health state costs and including antiviral treatment costs for underlying HBV infection (Section 4.2.10).	Health state costs were included for the F2 and F3 states.	Health state costs are excluded for the F2 and F3 states.	-£792
Additional issue: Removing the F4 health state costs and including antiviral treatment costs for underlying HBV infection (Section 4.2.10)	Health state costs were included for the F4 state.	Health state costs are excluded for the F4 state.	-£292
Additional issue: Using the observed trial data to estimate transition probabilities in the economic model for bulevirtide and BSC (Section 4.2.5.2)	TPs were estimated using external literature.	The EAG's preferred base-case approach of using the observed trial data to estimate TPs is applied.	-£670

Note: The analyses do not reflect the impact of the revised PAS post-TE.

Table 5: Updated cost-effectiveness results (Company base-case post-Technical Engagement) – without severity modifier

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	8.31	[redacted]	-			
Bulevirtide	[redacted]	13.90	[redacted]	[redacted]	5.59	[redacted]	£33,134

Note: Includes revised PAS approved by NHSE&I and PASLU post-TE.

Table 6: Updated cost-effectiveness results (Company base-case post-Technical Engagement) – including severity modifier of 1.2

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	8.31	[redacted]	-			
Bulevirtide	[redacted]	13.90	[redacted]	[redacted]	5.59	[redacted]	£27,612

Note: Includes revised PAS approved by NHSE&I and PASLU post-TE.

References

1. National Institute for Health and Care Excellence. Hepatitis B (chronic): diagnosis and management | Guidance | NICE [Internet]. 2017 [cited 2021 Oct 26]. Available from: https://www.nice.org.uk/guidance/cg165/ifp/chapter/drug-treatment

2. Lampertico P, Agarwal K, Berg T, Buti M, Janssen HLA, Papatheodoridis G, et al. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol [Internet]. 2017 Aug 1 [cited 2021 Oct 26];67(2):370–98. Available from: https://pubmed.ncbi.nlm.nih.gov/28427875/

3. GSI - Data on file. MYR 301 Clinical Study Report. 2022;

4. Spaan M, Carey I, Bruce M, Shang D, Horner M, Dusheiko G, et al. Hepatitis delta genotype 5 is associated with favourable disease outcome and better response to treatment compared to genotype 1. J Hepatol [Internet]. 2020;72(6):1097–104. Available from: http://dx.doi.org/10.1016/j.jhep.2019.12.028

5. Cross TJS, Rizzi P, Horner M, Jolly A, Hussain MJ, Smith HM, et al. The increasing prevalence of hepatitis delta virus (HDV) infection in South London. J Med Virol [Internet]. 2008 Feb [cited 2021 Nov 16];80(2):277–82. Available from: https://pubmed.ncbi.nlm.nih.gov/18098143/

6. William Tong CY, Asher R, Toby M, Ngui SL, Tettmar K, Ijaz S, et al. A re-assessment of the epidemiology and patient characteristics of hepatitis D virus infection in inner city London. J Infect [Internet]. 2013 Jun [cited 2022 Aug 15];66(6):521–7. Available from: https://pubmed.ncbi.nlm.nih.gov/23466596/

7. El Bouzidi K, Elamin W, Kranzer K, Irish DN, Ferns B, Kennedy P, et al. Hepatitis delta virus testing, epidemiology and management: a

multicentre cross-sectional study of patients in London. J Clin Virol [Internet]. 2015 May 1 [cited 2022 Aug 15];66:33–7. Available from: https://pubmed.ncbi.nlm.nih.gov/25866333/

8. Jackson C, Gunson RN, Bradley-Stewart A, Bennett S, Black H, Kennedy N, et al. Epidemiology and patient characteristics of hepatitis D virus infection in the West of Scotland 2011-2016. J Viral Hepat [Internet]. 2018 Nov 1 [cited 2022 Jun 20];25(11):1395–6. Available from: https://pubmed.ncbi.nlm.nih.gov/29851188/

9. Bigogno CM, Falahieh RR, Ho KMA, Jeffrey-Smith A, Jones M, Usai C, et al. The genetic landscape of hepatitis delta virus infection. Clin Med [Internet]. 2020 Mar 1 [cited 2022 Aug 23];20(Suppl 2):S101. Available from: https://pubmed.ncbi.nlm.nih.gov/32409407/

10. GSI - Data on file. Advisory Board Report. 2022.

11. National Institute for Health and Care Excellence (NICE). NICE Multiple Technology Appraisal ID1276 Selective internal radiation therapies for treating hepatocellular carcinoma. 2019;

12. Papatheodoridis G V., Chrysanthos N, Hadziyannis E, Cholongitas E, Manesis EK. Longitudinal changes in serum HBV DNA levels and predictors of progression during the natural course of HBeAg-negative chronic hepatitis B virus infection. J Viral Hepat. 2008;15(6):434–41.

13. Fattovich G. Natural history and prognosis of hepatitis B [Internet]. Vol. 23, Seminars in Liver Disease. Copyright © 2002 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA. Tel.: +1(212) 584-4662; 2003 [cited 2021 Oct 26]. p. 47–58. Available from: http://www.thieme-connect.com/products/ejournals/html/10.1055/s-2003-37590

14. Farci P, Niro GA, Zamboni F, Diaz G. Hepatitis d virus and hepatocellular carcinoma. Viruses. 2021;13(5).

15. Jang TY, Wei YJ, Liu TW, Yeh ML, Liu SF, Hsu CT, et al. Role of hepatitis D virus infection in development of hepatocellular carcinoma among chronic hepatitis B patients treated with nucleotide/nucleoside analogues. Sci Rep [Internet]. 2021;11(1):1–7. Available from: https://doi.org/10.1038/s41598-021-87679-w

Bulevirtide for treating chronic hepatitis D

EAG response to company technical engagement comments

September 2022

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 13/37/00.

1 Introduction

This document provides the Evidence Assessment Group's (EAG's) critique of the company's response to the key issues raised in the external assessment report (EAR) for the appraisal bulevirtide for treating chronic hepatitis D (CHD).

2 EAG's critique of company comments to key issues

2.1 Key issue 1: Generalisability of trial population to the narrower population focused on by the company

The company has focused their submission on a subpopulation of the key trial (MYR 301); patients with CHD who have compensated liver disease and evidence of significant fibrosis (METAVIR stage greater than or equal to F2), whose disease has responded inadequately to IFN-based therapy, or who are ineligible to receive IFN-based therapy due to intolerance or contraindication. In the EAG report, the EAG highlighted the uncertainty around the generalisability and internal integrity of the full trial population compared with the narrower population the company has focused on.

In contrast to the evidence presented in the company submission, which focused on the subgroup of patients in MYR 301 with prior IFN-based therapy, the company has in their technical engagement (TE) response clarified that they consider the full trial population to be generalisable to the narrower population focused on by the company. The EAG partially agrees, while the trial did not capture if participants were intolerant of or for whom IFN-based therapy was contraindicated, most patients in the trial who had not received prior IFN-based therapy are likely to be intolerant or contraindicated.

The EAG's main concern about the trial population's generalisability to the population focused on by the company, is the inclusion of and potential imbalance between the treatment arms in patients without significant fibrosis, i.e., with METAVIR stage F0 and F1. As described in the EAG report METAVIR fibrosis stage data were missing for a large proportion of patients, and for participants with data available there was a relatively large imbalance between the treatment arms with a larger number of patients with the lower stages of fibrosis (F0 and F1) in the bulevirtide arm. The EAG hypothesises that it may be easier for patients with lower METAVIR fibrosis stage (F0 or F1) to achieve biochemical response as they are likely to be closer to the ALT normalisation threshold. This would cause a potential overestimate of the efficacy of bulevirtide 2 mg compared with BSC in the full trial population compared with patients with METAVIR fibrosis stage of F2 or above, i.e. the population the company is focusing on.

The company highlights that the model is driven by the achievement of a combined response rather than biochemical response, but the EAG notes that the limiting factor for the combined response is the number of patients with biochemical response as this was lower than the number of virological

responders. That is, any imbalance in the number of patients with METAVIR stage F0 and F1 may bias the biochemical response data and therefore also the combined response data.

To address the potential influence of the inclusion and imbalance of patients with without evidence of significant fibrosis (METAVIR F0 and F1), the EAG requested that the company provide a scenario analysis focusing on the subgroup of patients with cirrhosis at baseline. In the CS and the economic model, the company defined people with cirrhosis as METAVIR fibrosis stage F4 (CS, B.1.1. Decision problem Table 1, B.3.2.2 Model structure). However, the company later clarified that cirrhosis status of patients in the trial was determined according to the clinical judgement of the investigators based on clinical, histological and other diagnostic measures, and available METAVIR data, from the CSR (Table 10979.3) and as presented in the company's TE response (Table 1.1), indicate a very poor correlation between METAVIR stage F4 and the clinically defined cirrhosis.

Due to the poor overlap between the clinical definition of cirrhosis and that based on METAVIR stage, on reflection, the EAG agrees that a scenario analysis looking at the cirrhotic subgroup in MYR 301, i.e. using the clinical definition of cirrhosis rather than METAVIR stage F4, will not adequately resolve the issue of the inclusion and potential imbalance of patients without significant fibrosis (F0 and F1) as data are not available, based on a clinical definition, for patients with significant fibrosis but who has not developed cirrhosis.

Therefore, the uncertainty remains around if and how the inclusion and potential imbalance of patients without significant fibrosis in the MYR 301 trial may affect the relative efficacy of bulevirtide compared with delayed treatment in the trial and the generalisability of the trial results to the narrower population, which is the focus of the company's submission. In addition, this raises the question of how the narrower population of patients with significant fibrosis will be identified in clinical practice when a large proportion of patients choose not to have a biopsy enabling METAVIR staging and when there seems to be a very poor correlation between METAVIR fibrosis staging and the clinical definition of significant fibrosis.

2.2 Key issue 2: Generalisability of trial population to UK patients

The company provided additional evidence for UK specific baseline characteristics in their technical engagement comments (Table 2.1 of the company's response). However, the EAG considers that the data provided by the company further highlights the uncertainty around the key parameters of age

and cirrhosis status at baseline as age varied between 35 to 40 years and where baseline cirrhosis was reported, it ranged from 26% to 59%.

In response to technical engagement, the lead investigator of a study of the epidemiology of HDV infection in the UK (funded by the company) stated that data relevant to the baseline characteristics of HDV patients in the UK will be available in mid-September 2022. Given that the study collected data from 10 virology laboratories in the UK in the last 10 years, the EAG anticipates this to provide the most robust and representative source of data to inform baseline characteristics in the model for CHD patients. Thus, the EAG recommends that the company includes a scenario analysis using these data before the ACM.

However, if the new UK epidemiological data are not available before the ACM, as discussed in Section 4.2.2 of the EAR, the EAG recommends that the committee's clinical experts assess the plausibility of the population characteristics using the published data in the company's base case as well as the using baseline characteristics from MYR 301 (Table 1). The EAG highlights that the choice of source for baseline characteristics has a significant impact on the assumptions made around the severity modifier that may be applied in the cost-effectiveness analysis (please refer to Section 4 of this report for results).

Table 1. Baseline characteristics data and sources

Parameter	Company base case – sourced from literature	MYR 301
Age at diagnosis	35 years	42 years
Cirrhotic	60%	47%

2.3 Key issue 3: Uncertainty in the extrapolations beyond the observed trial data

The EAG's key concerns regarding extrapolations beyond observed data in the model were around:

1. The company's method for extrapolating 48-week data from the trial for one additional cycle in the model (i.e., up to 72 weeks). The EAG considered the company's extrapolations of biochemical response to be flawed and considered that a more robust approach would have been to only include the 48-week trial data in the model (see Section 4.2.5 of the EAG report).

2. The treatment duration with bulevirtide in the trial and in the model. The EAG noted the company's statement that treatment with bulevirtide should be continued as long as

associated with a clinical benefit, while the SmPC states that discontinuation of treatment should be considered in case of loss of virological and biochemical response.

In the MYR 301 trial, participants were reportedly scheduled to continued bulevirtide treatment up to 144 weeks. However, in the economic model, the company assumed that:

- Partial responders who have not achieved a complete response continue treatment up to week 72 but discontinue treatment then (if they don't achieve a complete response). The EAG notes that in MYR 301, treatment is likely to have carried on for a longer period of time for these patients.
- Non-responders to treatment at week 48 discontinue treatment, however, the company did not provide a clear justification for this assumption and the EAG is unclear if 48 weeks was chosen due to this being the same data cut-off period available for MYR 301; or for any other reason. The EAG remains unclear if in MYR 301 non-responders discontinued treatment at 48 weeks.

Given that patients from the MYR 301 study continued to be followed up and that data for 96 weeks of treatment are anticipated to become available in [redacted], the EAG noted that reliable observed data to populate the model for an additional 2 cycles would become available soon. Furthermore, the EAG noted that duration of complete response and duration of treatment in the economic model would need careful re-assessment when the 96-week follow-up data are available for MYR 301. Duration of treatment and time to response in the trial will need to be investigated when the more mature data are available, as it might be that, for example, non-responders at week 48 continued treatment and became responders later in the trial (if all patients continued treatment for 144 weeks as planned).

In response to the EAG's concerns, the company refitted the trial data with a nonlinear least squares (NLSE) regression, with a binomial link function. The EAG agrees with the company that the NLSE regression provides a better visual fit to the observed trial data for complete response (see Issue 3 on company's response to TE document) than the company's originally used EMAX function (see Section 4.2.5 of the EAG report). Nonetheless, while the NLSE results provide a better option than the EMAX results in extrapolating data up to 72 weeks in the model, the EAG notes that the observed 96-week data, once available, will still be a more robust option. Crucially, the company did not address any of the concerns raised by the EAG regarding treatment duration/discontinuation in MYR 301 and in the economic model. The EAG maintains its view that duration of complete

response and duration of treatment in the economic model will need careful re-assessment when the 96-week follow-up data are available for MYR 301.

2.4 Key issue 4: Modelling of hepatocellular carcinoma

During TE, the EAG noted that patients entering the hepatocellular carcinoma (HCC) state in the model could only remain in the HCC state or transition to the liver transplant (LT) state. The EAG was unclear on the clinical plausibility of this assumption, as the Barcelona Clinic Liver Cancer staging and treatment recommendations for HCC (as reported in TA551) suggest that patients, especially in the earlier stages of HCC, can be cured through other procedures such as resection or ablations. The EAG was concerned that the company's assumption, if not clinically plausible, was biased towards bulevirtide as a higher proportion of patients in the BSC arm of the model experience HCC and remain in that same state, experiencing very high costs and a low utility value. Therefore, the EAG recommended that the company validated this assumption at TE and included a scenario analysis in the model where a proportion of HCC patients could transition to a cure or a progression-free state of the disease.

In response to the EAG's concerns, the company sought clinical expert advice on HCC in CHD patients. The company reported that one of the clinical experts stated that the proportion of CHD patients eligible for procedures such as resection or ablations is approximately 10% to 20%, as most CHD patients have significant portal hypertension. With regards to proportions achieving cure, clinical experts agreed that this would be approximately 30% of patients.

The company included a scenario analysis where 30% of HCC patients were assumed to be cured of the disease. The company also implemented a reduction in mortality associated with the HCC state for all patients (cured and non-cured), by decreasing the mortality rate in the HCC state (56%) by the equivalent percentage of patients assumed to be cured from HCC. Thus, in the company's scenario, mortality for all HCC patients dropped by 30%, and was estimated to be 39.2%. This is the equivalent to assuming that cured HCC patients have a 0% probability of death, which is a conservative assumption.

The company also assumed that cured patients have a higher utility value. For those patients who remain uncured, the original health state utility of 0.52 was applied, while for the proportion who are cured, a utility of 0.70 was applied. The company sourced the 0.70 utility value from the progression-free survival health state utility value that was applied for the standard of care arm in

NICE TA688 (selective internal radiation therapies for treating HCC). The EAG disagrees with the use of the 0.70 utility as this is lower than the utility value used in the company's base case for patients in the F4 states (or below), where the lowest value of 0.76 (or 0.81 in the EAG's preferred utility analysis) was assumed for non-responders with compensated cirrhosis (F4 METAVIR state). The EAG considers that patients cured from HCC should at least have the same utility value as non-responders in the compensated cirrhosis state of the model. Therefore, the EAG conducted a scenario analysis where this is assumed in the model and reports this is section 4.

3 Company updated results

The company accepted some of the EAG's preferred assumptions, but several issues remain unresolved. The company agreed with the EAG's following changes to the model (initially reported in the EAR):

1. Use of the observed trial data to estimate TPs in the economic model for bulevirtide and BSC – Section 4.2.5.2 of EAR.
2. Removing the F2 and F3 health state costs and including antiviral treatment costs for underlying HBV infection – Section 4.2.10 of EAR.
3. Removing the F4 health state costs and including antiviral treatment costs for underlying HBV infection – Section 4.2.10 of EAR.

Additionally, the company corrected the calculations around the annual probability of progression from one F-stage to the next from 15.07% to 12.53% and used the NLSE regression to extrapolate treatment effectiveness instead of the original EMAX function. Furthermore, the company made a change to the model which has not been properly justified or explained, where the company changed the resource use associated with disease monitoring costs as "further clinical expert opinion was received" during TE.

The company also updated their patient access scheme (PAS) from [redacted]. The company's updated cost effectiveness results, with the updated PAS are reported in Table 2.

Table 2. Company's deterministic base case results post technical engagement

Interventions	Total Costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)	ICER (£/QALY) - 1.2 severity weighting
BSC	[redacted]	8.31	[redacted]	-				
Bulevirtide	[redacted]	13.90	[redacted]	[redacted]	5.59	[redacted]	£33,133	£27,611

Abbreviations: BSC, best supportive care; EAG, evidence assessment group; ICER, incremental cost-effectiveness ratio; inc, incremental; LY, life years; N/A, not applicable; QALY, quality adjusted life year

4 EAG preferred assumptions

Whereas the EAG agrees with the three changes listed above made by the company (originally requested by the EAG), the EAG considers the company has not presented any new evidence that resolves the outstanding issues presented below. The following assumptions are included in the EAG base case and results are presented in Table 3 and Table 4, with the company updated PAS included:

- Assuming that 48 weeks is the maximum timeframe for assessing final response to treatment, and treatment effectiveness is not extrapolated – Section 4.2.4 of the EAR.
- Estimation of the probability of HCC from the F2-F4 states according to Romeo[1] and Kushner[2] – Table 25, Section 4.2.5.3.1 of the EAR.
- Estimation of the probability of fibrosis progression from the F2-F4 states according to Romeo[1] – Table 26, Section 4.2.5.3.1 of the EAR.
- Assuming that CRs have the same probability as PRs (which is lower than the probability of NRs) of developing HCC, instead of having a 0% probability of HCC – Section 4.2.5.3.1 of the EAR.
- Using the [redacted] utility value to estimate the quality of life for NRs and PRs in the F-states, together with assuming a [redacted] utility value for CRs; and assuming that PLT patients experience a 0.87 utility after transplant – Section 4.2.8 of the EAR.
- Adjusting utilities as per Ara and Brazier[3] – Section 4.2.8 of the EAR.
- Removing the company's new changes made to resource use in the model.
- Assuming that 30% of HCC patients get cured from HCC and accrue a utility of 0.81.

The model key drivers remain the source of the baseline characteristics (i.e., the MYR 301 trial or external literature) and adjusting the utilities for patients' age as per Ara and Brazier.[3] The EAG-preferred ICERs range from £33,644 when external literature is used to estimate patient's baseline characteristics to £45,216 per QALY gained when the MYR 301 population is used.

The company assumed that 60% of patients at baseline had CC, while the equivalent proportion in the MYR 301 trial was 47%. The company also assumed that patients were 35 years old at baseline, while this was 42 years in the trial. These assumptions have a considerable impact on the final ICER and thus the EAG recommends that: 1) the company presents a scenario analysis with the data arising from the study on the epidemiology of HDV infection in the UK; 2) the committee seeks clinical expert opinion to validate these assumptions.

The also EAG maintains its view that duration of complete response and duration of treatment in the economic model will need careful re-assessment when the 96-week follow-up data are available for MYR 301.

Table 3. EAG's preferred model assumptions - deterministic

Preferred assumption	Section in EAR	Cumulative ICER (£/QALY)	Cumulative ICER (£/QALY) - 1.2 severity weighting
Company revised base case post technical engagement	-	£33,133	£27,611
Assuming that 48 weeks is the maximum timeframe for assessing final response to treatment, and treatment effectiveness is not extrapolated	Section 4.2.4.	£32,610	£27,175
Estimation of the probability of HCC from the F2-F4 states according to Romeo[1] and Kushner[2]	Table 20, Section 4.2.5.3.1	£33,257	£27,714
Estimation of the probability of fibrosis progression from the F2-F4 states according to Romeo	Table 21, Section 4.2.5.3.1	£34,201	£28,501
Assuming that CRs have the same probability as PRs (which is lower than the probability of NRs) of developing HCC, instead of having a 0% probability of HCC.	Section 4.2.5.3.1	£35,786	£29,822
Using the 0.81 utility value to estimate the quality of life for NRs and PRs in the F-states, together with assuming a [redacted] utility value for CRs; and assuming that PLT patients experience a [redacted] utility after transplant	Section 4.2.8.	£36,967	£30,806
Adjusting utilities as per Ara and Brazier	Section 4.2.8.	£40,114	£33,429
Removing the company's new changes made to resource use in the model.	Section 4 of this report	£40,141	£33,451
Assuming that 30% of HCC patients get cured from HCC and accrue a utility of 0.81.	Section 2.4 of this report	£40,372	£33,644
EAG preferred base case ICER – published baseline characteristics	**-**	**£40,372**	**£33,644**
EAG preferred base case ICER - MYR 301 baseline characteristics	Section 4.2.2.	**£48,097**	N/A - estimated severity weighting using MYR 301 is 1.

Abbreviations: EAG, Evidence Assessment Group; EAR, external assessment report; ICER, incremental cost-effectiveness ratio; N/A, not applicable; QALY, quality adjusted life year

Table 4. EAG's deterministic base case results post technical engagement

Interventions	Total Costs (£)	Total LYG*	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)	ICER (£/QALY) - 1.2 severity weighting
Published baseline characteristics								
BSC	[redacted]	14.58	[redacted]	-	-	-	-	-
Bulevirtide	[redacted]	23.87	[redacted]	[redacted]	9.30	[redacted]	£40,372	£33,644
MYR 301 baseline characteristics								
BSC	[redacted]	16.14	[redacted]	-	-	-	-	-
Bulevirtide	[redacted]	23.70	[redacted]	[redacted]	7.56	[redacted]	£48,097	N/A

Abbreviations: BSC, best supportive care; EAG, evidence assessment group; ICER, incremental cost-effectiveness ratio; inc, incremental; LY, life years; N/A, not applicable; QALY, quality adjusted life year

*undiscounted

5 References

1. Romeo R, Del Ninno E, Rumi M, et al. A 28-Year Study of the Course of Hepatitis Δ Infection: A Risk Factor for Cirrhosis and Hepatocellular Carcinoma. *Gastroenterology* 2009;136(5):1629-38. doi: 10.1053/j.gastro.2009.01.052
2. Tatyana Kushner MS, David Kaplan. Delta Hepatitis within the Veterans Affairs Medical System in the United States: Prevalence, Risk Factors, and Outcomes. *Journal of Hepatology* 2015;63(3):586-92.
3. Ara R, Brazier J. Deriving an algorithm to convert the eight mean SF-36 dimension scores into a mean EQ-5D preference-based score from published studies (where patient level data are not available). *Value Health* 2008;11(7):1131-43. doi: 10.1111/j.1524-4733.2008.00352.x [published Online First: 2008/05/21]

Bulevirtide for treating chronic hepatitis D

Addendum to EAG response to company technical engagement comments

October 2022

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 13/37/00.

1 Introduction

This document provides the additional results requested by NICE resulting from the Evidence Assessment Group's (EAG's) critique of the company's response to technical engagement (TE).

2 Company updated results

The company's updated deterministic cost effectiveness results, with the updated PAS are reported in Table 1, while the company probabilistic updated results are reported in Table 2.

Table 1. Company's deterministic base case results post technical engagement

Interventions	Total Costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	Inc. QALYs - 1.2 severity weighting	ICER (£/QALY)	ICER (£/QALY) - 1.2 severity weighting
BSC	[redacted]	[redacted]	-	-			
Bulevirtide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,133	£27,611

Abbreviations: BSC, best supportive care; EAG, evidence assessment group; ICER, incremental cost-effectiveness ratio; inc, incremental; LY, life years; N/A, not applicable; QALY, quality adjusted life year

Table 2. Company's probabilistic base case results post technical engagement

Interventions	Total Costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	Inc. QALYs - 1.2 severity weighting	ICER (£/QALY)	ICER (£/QALY) - 1.2 severity weighting
BSC	[redacted]	[redacted]	-	-			
Bulevirtide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,693	£28,078

Abbreviations: BSC, best supportive care; EAG, evidence assessment group; ICER, incremental cost-effectiveness ratio; inc, incremental; LY, life years; N/A, not applicable; QALY, quality adjusted life year

3 EAG preferred assumptions

Table 3 reports the EAG's deterministic ICERs, including all EAG's preferred assumptions (as detailed in Section 4 of the EAG response to TE), when external literature is used to estimate patients' baseline characteristics, and when the MYR 301 population is used. Table 4 provides the equivalent probabilistic results.

Table 3. EAG's deterministic base case results post technical engagement

Interventions	Total Costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	Inc. QALYs - 1.2 severity weighting	ICER (£/QALY)	ICER (£/QALY) - 1.2 severity weighting
Published baseline characteristics							
BSC	[redacted]	[redacted]	-	-	-	-	-
Bulevirtide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£40,372	£33,644
MYR 301 baseline characteristics							
BSC	[redacted]	[redacted]		-	-	-	-
Bulevirtide	[redacted]	[redacted]	[redacted]	[redacted]	N/A	£48,097	N/A

Abbreviations: BSC, best supportive care; EAG, evidence assessment group; ICER, incremental cost-effectiveness ratio; inc, incremental; LY, life years; N/A, not applicable; QALY, quality adjusted life year

Table 4. EAG's probabilistic base case results post technical engagement

Interventions	Total Costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	Inc. QALYs - 1.2 severity weighting	ICER (£/QALY)	ICER (£/QALY) - 1.2 severity weighting
Published baseline characteristics							
BSC	[redacted]	[redacted]	-	-			
Bulevirtide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£41,167	£34,306
MYR 301 baseline characteristics							
BSC	[redacted]	[redacted]	-	-	-	-	-
Bulevirtide	[redacted]	[redacted]	[redacted]	[redacted]	N/A	£48,688	N/A

Abbreviations: BSC, best supportive care; EAG, evidence assessment group; ICER, incremental cost-effectiveness ratio; inc, incremental; LY, life years; N/A, not applicable; QALY, quality adjusted life year

4 Exploratory analysis

In response to NICE's request, the EAG undertook two additional exploratory sensitivity analysis, which were originally discussed in the EAG report. Results from the exploratory analysis are reported in Table 5 and Table 6, with the company's updated PAS. Results represent the impact on the final ICER resulting from the EAG's preferred options (reported in Table 3 and Table 4 above).

1. Assuming that responders in the HCC health state carry on with bulevirtide treatment – Section 4.2.10 of the EAG report
2. Removing the utility gain associated with being a CR – Section 4.2.8. of the EAG report

Table 5. Exploratory analysis 1

Interventions	Total Costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	Inc. QALYs - 1.2 severity weighting	ICER (£/QALY)	ICER (£/QALY) - 1.2 severity weighting
Published baseline characteristics							
BSC	[redacted]	[redacted]	-	-	-	-	-
Bulevirtide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£40,813	£34,012
MYR 301 baseline characteristics							
BSC	[redacted]	[redacted]	-	-	-	-	-
Bulevirtide	[redacted]	[redacted]	[redacted]	[redacted]	NA	£48,498	N/A

Abbreviations: BSC, best supportive care; EAG, evidence assessment group; ICER, incremental cost-effectiveness ratio; inc, incremental; LY, life years; N/A, not applicable; QALY, quality adjusted life year

Table 6. Exploratory analysis 2

Interventions	Total Costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	Inc. QALYs - 1.2 severity weighting	ICER (£/QALY)	ICER (£/QALY) - 1.2 severity weighting
Published baseline characteristics							
BSC	[redacted]	[redacted]	-	-	-	-	-
Bulevirtide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£44,406	£37,255
MYR 301 baseline characteristics							
BSC	[redacted]	[redacted]	-	-	-	-	-
Bulevirtide	[redacted]	[redacted]	[redacted]	[redacted]	N/A	£54,223	N/A

Abbreviations: BSC, best supportive care; EAG, evidence assessment group; ICER, incremental cost-effectiveness ratio; inc, incremental; LY, life years; N/A, not applicable; QALY, quality adjusted life year

NICE National Institute for Health and Care Excellence

Data on the epidemiology of HDV infection in the UK

This document details summary demographic data (median age) for virology laboratories in the UK undertaking any form of HDV testing over the past 10 years. Data were provided by study investigators at UKHSA to NICE in October 2022. Data relate to the key issue “Generalisability of trial population to UK patients”, committee slides 21-22.

- Median age at first Ab positive result [redacted]
- RNA data – still waiting for data from UCL but have age for [redacted]
- Median age at first RNA positive result [redacted]
- Median age at last RNA positive result [redacted]– for some only tested once the first and last RNA will be the same.