Single Technology Appraisal

Bulevirtide for treating chronic hepatitis D [ID3732]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Bulevirtide for treating chronic hepatitis D [ID3732]

Contents:

The following documents are made available to stakeholders:

1. **Response to consultee, commentator and public comments on the Draft Guidance**

2. **Comments on the Draft Guidance from Gilead**

3. **Consultee and commentator comments on the Draft Guidance** from:
   a. NHS England

4. **External Assessment Group critique of company comments on the Draft Guidance**

5. **External Assessment Group review of PAS price change**

6. **Company response to External Assessment Group critique**

7. **External Assessment Group critique of company response on the Draft Guidance**

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

Appraisal title

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE 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 submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Company	Gilead	Summary conclusions are as follows: **1. The company's proposed positioning in people with METAVIR stage ≥F2 (Topic 1)** • The Company's proposed positioning for bulevirtide aligns with existing National Institute for Health and Care Excellence (NICE) clinical guideline (CG) 165. • Subgroup analysis of patients in MYR 301 in METAVIR fibrosis stages ≥F2 according to equivalent FibroScan cut-offs were conducted; the majority of MYR 301 patients ([redacted])[1] had a liver stiffness measurement consistent with METAVIR ≥F2 at baseline. The subgroup analysis and overall population (full analysis set) is therefore relevant to the decision problem. Response rates in the subgroup analysis are consistent with response rates in the overall population (presented in the Company's original submission) further demonstrating the efficacy of bulevirtide in patients with a high unmet need. • Cost-effectiveness analysis using response data from the subgroups defined by liver stiffness demonstrate the incremental cost-effectiveness ratio (ICER) to be robust and the ICER for bulevirtide ranging from £24,985 to £27,295 per quality-adjusted life year (QALY) gained when considering the 1.2 severity modifier. **2. The mean age of people diagnosed with hepatitis D in the UK (Topic 2)** • The mean age of people diagnosed with hepatitis D in the UK determined by the UK Health Security Agency (UKHSA) does not alter eligibility for a severity weight when applied to the company base-case. The mean age of people with hepatitis delta virus (HDV) is estimated to be 36.9 years, however the data is skewed meaning that the median age (35.0 years) is a more appropriate measure of average age and is consistent	Comment noted. Thank you for providing this summary of your response.

[1] Based on a transient elastography of ≥8.0 kPA.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			with the average age used in the Company's base case analysis (35.1 years, as per Spaan *et al.,* 2020) (1). • UKHSA data demonstrates that the majority of patients (55%) with hepatitis D are young, being 36 years of age or less[2] (2). • Cost-effectiveness analysis using the UKHSA data further demonstrates that there is a significant QALY shortfall amongst people living with CHD compared to the expected future health without the condition over the remaining lifetime of the patient; meaning bulevirtide qualifies for the 1.2 severity modifier. • Bulevirtide is a cost-effective treatment option compared to best supportive care (BSC); the ICER ranging from £27,031 to £27,452 per QALY gained when considering the 1.2 severity modifier. **3. Model progression/regression rates (Topic 3)** • A low but not zero risk of progression through fibrosis stages for combined responders was explored in the model, resulting in a negligible impact on the Company's base-case ICER (+£513). • A low but not zero risk of progression to hepatocellular carcinoma (HCC) for combined responders was explored in the model, resulting in a negligible impact on the Company's base-case ICER (+£515). • A lower probability of fibrosis regression for combined responders in the model had a relatively modest impact on the Company's base-case ICER (+£907). Regression rates in the model were informed by observed responses to antiviral treatments in chronic hepatitis B (CHB) and chronic hepatitis delta (CHD) patients in the real-world. Given that these rates of regression were informed by real-world evidence in patients with viral hepatitis, we do not consider scenario analyses for lower regression rates requested by committee to be realistic. • The Company's base-case ICERs range from £27,544 to £27,938 per QALY gained across these scenario	

[2] The 1.2x QALY modifier threshold in the EAG's model is 36.49 years.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			analyses (including the 1.2 severity modifier). **4. Treatment duration beyond 48 weeks in MYR 301 (Topic 4)** • The Company has carried out a scenario analysis which explores the impact of continuing treatment in patients who develop HCC and relaxing the treatment continuation criteria to the achievement of virologic response only; the associated ICER was £27,031 per QALY gained (including the 1.2 severity modifier). • While assuming the same continuation rules for virologic and combined responders increases the ICER, we note that clinicians were unsure that virologic responders would have the same continuation rules and that this may only apply to specific cases. The associated ICERs were £32,470 to £32,889 (including the 1.2 severity modifier). • The more realistic scenario that patients with virus eradication could discontinue treatment substantially offsets any effect from a minority of virologic responders continuing treatment; the associated ICER were £27,031 to £32,889 per QALY gained (including the 1.2 severity modifier). **5. The size of utility gain for combined responders (Topic 5)** • NICE methods guidance stipulates that where possible utilities from the technology's clinical trials should be used in the economic model. The Company's choice of regression model for generating utilities was underpinned by observed ceiling effects from the MYR 301 data. • Utility gains for patients with sustained virologic response (SVR) in other hepatitis technology appraisals has been slightly lower (different by ≤0.02) than that observed for combined responders in MYR 301, however this may be explained by differences in the type of hepatitis infection and population. • The impact on the ICER of varying the size of the utility gain for combined responders was explored by assuming 75% and 50% of the current MYR 301 responder utility gain; the associated ICER were £27,642 and £28,282 respectively (including the 1.2 severity modifier).	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			6. The long-term survival for people on standard care, in the absence of bulevirtide (Topic 6) • The Company has validated the progression and survival rates predicted by the economic model with those in the published CHD literature by comparing Kaplan-Meier plots with survival plots extracted from the model. • There was close alignment between the model predictions and the published literature, with divergence only observed at later timepoints where costs and outcomes are discounted. • The analysis demonstrates that that Company's base-case assumptions associated with the natural history of CHD are appropriate. The NICE health technology evaluation manual (2022) notes that a higher degree of uncertainty regarding estimates of cost-effectiveness is acceptable for health technologies for which evidence generation is particularly difficult, specifically for rare diseases and innovative technologies (see section 6.2.34, pp. 157). The majority of the scenarios requested by the Committee have a relatively modest impact on the ICER. In the majority of cases the ICER associated with bulevirtide remains with the £20,000 to £30,000 per QALY gained range normally considered a cost-effective use of NHS resources. This is particularly compelling given that CHD is a rare disease and bulevirtide is an innovative first-in-class treatment with GB orphan drug designation. The Company accepts a number of the External Assessment Group (EAG) preferred assumptions (the majority of which were not discussed in part 1 of the appraisal committee meeting) and is willing to adjust its preferred base case accordingly. **The Company has therefore updated its current base case assumptions with the following changes:** i. Average age of people diagnosed with hepatitis D in the UK based on UKHSA median age of 35.0 years, further supported by Spaan *et al.* (2020). ii. Treatment stopped for those with convincing evidence of virus eradication (see section 3.11 of the ACD). Clinical experts confirmed that patients with convincing evidence of virus eradication, treatment would likely be stopped. This scenario had previously been conservatively excluded from the Company base-case, but as the Company is aware that this is a feasible scenario in UK clinical practice, this has now been included in the post-committee base-case. iii. MYR 301 data not extrapolated beyond Week 48; note this is a conservative assumption considering the	

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>
observed trend of increasing response rates across the first 48 weeks of treatment with bulevirtide.

iv. Age-related utility decrements included.

v. Health state utilities based on MYR 301.

vi. Post-liver transplant utility value set to MYR 301.

vii. Assuming that patients who develop HCC remain on bulevirtide.

The revised Company base case cost effectiveness results are presented in Table 1. It can be seen that the severity-weighted ICER lies below the willingness-to-pay threshold of £30,000 per QALY gained using a severity modifier of 1.2x, demonstrating that bulevirtide not only provides significant benefits in terms of improved patient prognosis, but is a cost-effective treatment for the NHS.
Table 1: Company’s ACD revised base case cost-effectiveness estimates
<table>
<tr><th>Interventions</th><th>Total costs (£)</th><th>Total QALYs</th><th>Incremental costs</th><th>Incremental QALYs</th><th>Incremental QALYs – 1.2 severity weighting</th><th>ICER</th><th>ICER - 1.2 severity weighting</th></tr>
<tr><td>BSC[3]</td><td>[redacted]</td><td>[redacted]</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Bulevirtide</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>£32,437</td><td>£27,031</td></tr>
</table>
The ICER does not reflect additional benefits associated with bulevirtide
The Committee noted in the ACD that there are several benefits of bulevirtide that were not captured by the QALY calculation.
Hepatitis D is a rare disease and bulevirtide is the first licensed treatment option for the treatment of CHD. The Committee were of the opinion that bulevirtide is an innovative treatment option which is well tolerated, and which addresses this unmet need. Bulevirtide is a first-in-class medicine with GB orphan designation (PLGB 50662/0002/OD1) and promising innovative medicines (PIM) designation. The Committee heard from clinical experts that bulevirtide represents a step change in the management of the CHD.
The Committee acknowledged that bulevirtide reduces the viral load in infected people thereby preventing the spread of infection; a significant benefit not captured by the QALY calculation. Additionally, the Committee heard from a patient advocacy group representative and clinicians concerning the stigma associated with blood-borne viruses. Clinical advisers have advised the Company that the introduction of a licenced treatment option such as bulevirtide is expected to bring about healthcare system-wide benefits as clinicians and patients will now have an effective treatment option such as encouraging HDV testing and reducing regional variation in practice. Early diagnosis and treatment of HDV is expected to positively impact health outcomes and reduce costs associated with healthcare
</td><td></td></tr>
</table>

[3] Please note that BSC results remain unchanged.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			resource use. Reducing and/or delaying the progression to more severe disease including decompensated cirrhosis (DCC), liver cancer, and liver transplant, is expected to result in a significant reduction to healthcare costs and a substantial QALY gain. In the appraisal committee meeting, the Committee acknowledged that HDV disproportionately affects some groups of people such as Black African people and economic migrants. The Company recognises that the pivotal registrational phase III study of bulevirtide, MYR 301, is ongoing. However, the Company is of the strong opinion that based on the totality of evidence, the uncertainty associated with an innovative treatment for a rare disease is proportionate; bulevirtide represents a cost-effective treatment option and should therefore be recommended.	
	Company	Gilead	**Topic 1 The Company's proposed positioning in people with METAVIR stage ≥F2** **ACD section 3.3** *"The company presented data from the full analysis set from MYR 301, which included people with all METAVIR fibrosis stages (F0 to F4), so it was unclear why the company positioned bulevirtide only for METAVIR stage F2 and above…"* **ACD section 3.4** *"METAVIR staging is done using a liver biopsy, which is invasive and carries a morbidity and mortality risk. Therefore, many people refuse this procedure… it would be useful for the company to present data using transient elastography rather than liver biopsy (METAVIR staging) to assess fibrosis"* **Company response:** • Existing NICE guidelines CG165 advise that peginterferon alfa-2a (PEG-IFN) should only be initiated in patients co-infected with hepatitis D "*who have evidence of significant fibrosis (METAVIR stage greater than or equal to F2 or Ishak stage greater than or equal to 3)*". The Company's proposed positioning for bulevirtide aligns with this. • Transient elastography (FibroScan) scores were collected for all patients in the MYR 301 study. We were able to identify subgroups of patients in MYR 301 in fibrosis stages greater than or equal to F2 (≥F2) according to published FibroScan cut-offs (≥7.25 kPa or ≥8.0 kPa) and found that [redacted]% of MYR 301 patients were ≥F2. • Scenario analyses demonstrate the ICER to be robust in the subgroup of patients with FibroScan scores considered to align with fibrosis stage ≥F2 in UK clinical practice. **1.1 Summary** The committee queried the Company's proposed positioning of bulevirtide for the treatment of CHD in adult patients with compensated liver disease and evidence of significant fibrosis (METAVIR stage ≥F2), given the METAVIR F-stage distribution of patients recruited to MYR 301. They further queried how patients with METAVIR stage ≥F2 would be identified in clinical practice. In section 1.2, we explain that the identification of patients with significant fibrosis is already required to identify patients eligible for treatment with peginterferon alpha-2a (PEG-IFN) in the UK and that	Comment noted. Thank you. The committee discussed this further at the second committee meeting. Its discussions and conclusions are reported in section 3.3, 3.4, 3.5 and 3.6 of the final draft guidance.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			this is based on transient elastography (FibroScan) score cut-off points. Liver stiffness, as measured by transient elastography (FibroScan) was collected for all patients enrolled onto the pivotal MYR 301 clinical study. As a result, it was possible to assign patients in MYR 301 to METAVIR fibrosis stages based on their FibroScan score in a manner aligned with UK clinical practice, and identify subgroups for patients with METAVIR stage ≥F2 according to their FibroScan score. When using this approach, we found that an overwhelming majority ([redacted]%) of MYR 301 patients at baseline in the bulevirtide 2 mg and delayed treatment arms would be deemed to be ≥F2 according to UK clinical practice. In summary, we have demonstrated that the proposed positioning of bulevirtide is in line with the existing NICE guideline CG165, that identification of patients in METAVIR fibrosis stage ≥F2 is feasible in clinical practice and that the MYR 301 data are generalisable to that population. Furthermore, in section 1.3 we undertake a scenario analysis in the model where we incorporate the responder data for MYR 301 patients identified as being ≥F2 according to both FibroScan and METAVIR score. The Company's ICERs remain largely unchanged in these scenarios, varying only slightly compared with the base case. **1.2 Identification of patients in METAVIR fibrosis stage ≥F2 in clinical practice** The treatment options for patients with chronic hepatitis delta (CHD) are limited. NICE guideline CG165 recommends that adults with chronic hepatitis B (CHB) and hepatitis delta infection, who have evidence of significant fibrosis (METAVIR stage ≥F2 or Ishak stage ≥3), should be offered a 48-week course of off-label PEG-IFN (3). Similarly, bulevirtide is proposed to treat adults with CHD with METAVIR stage ≥F2, albeit patients are required to have compensated liver disease and should not have responded well enough to a prior course of interferon-based therapy (hereafter referred to as IFN-based therapy), should have an intolerance to IFN-based therapy, or should have a contraindication to IFN-based therapy. To determine METAVIR stage, and thus level of liver fibrosis, patients are required to undergo a liver biopsy. However, as discussed in the draft guidance consultation, clinical experts highlighted that liver biopsy is an invasive procedure which carries a morbidity and mortality risk to the patient. As such, many patients refuse to undergo this procedure. Clinical experts explained that in clinical practice, transient elastography (FibroScan), a non-invasive test recommended in NICE guideline CG165 to assess liver disease in all adults diagnosed with chronic hepatitis B (CHB), is widely used to assess eligibility for PEG-IFN in CHD patients. Experts highlighted that they would like to use transient elastography to determine the patient eligibility for treatment with bulevirtide, as opposed to undertaking liver biopsy. FibroScan can identify significant fibrosis in patients with viral hepatitis and advanced liver disease to a good degree of accuracy (4, 5). A FibroScan threshold that corresponds to significant fibrosis (METAVIR stage ≥F2) in CHD has not yet been published, perhaps due to the orphan nature of the disease, and consultation with clinical experts confirms that heterogeneity exists regarding the appropriate cut-off value. In the absence of a clinical expert consensus, we conducted a literature search to identify potential cut-offs that could be applied to the Company's FibroScan data. Based on this literature search, we identified two thresholds. A meta-analysis by Qi *et al*., (2018) assessing the diagnostic accuracy of transient elastography in 7,808 CHB patients identified an optimal threshold value of ≥7.25 kPa at baseline to determine the presence of significant fibrosis (6). In addition, 2021 European Association for the Study of the Liver (EASL) clinical practice guidelines on non-invasive tests for evaluation of liver disease and severity and prognosis strongly recommend a FibroScan score of ≥8.0 kPa to confirm METAVIR fibrosis score ≥F2 (4). FibroScan scores were collected in the pivotal MYR 301 study in all patients at baseline and Week 48. We have utilised both literature cut-offs to define subgroups of patients with a METAVIR fibrosis score of ≥F2 given their FibroScan score. [redacted] and [redacted] of patients in the bulevirtide 2 mg and delayed treatment arms in MYR 301 had a	

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>
FibroScan score of ≥7.25 kPa and ≥8.0 kPa, respectively, indicating that an overwhelming majority of patients in MYR 301 study were in line with the proposed positioning in patients with a METAVIR fibrosis score of ≥F2.
Furthermore, we carried out a scenario analysis in the model using the response rates (both combined and virologic) of these subgroups of patients in fibrosis stage ≥F2. The response rates of the subgroups, compared with the overall population, are shown in Table 2: Results of the subgroup analyses for virologic response
. Results of the scenario analyses in the subgroups of patients with a transient elastography score aligned with METAVIR stage ≥F2 in UK clinical practice can be found below. We also present, alongside this, the results of the subgroup analysis based on the METAVIR score collected in MYR 301 (noting that biopsy data were unavailable for [redacted] of patients at baseline across the delayed treatment and bulevirtide 2 mg arms). The METAVIR scores may not be missing at random, given that more advanced patients may have been more likely to have had a liver biopsy in the past and may therefore have been less willing to have one as part of MYR 301. The results of both scenario analyses show the ICER to be robust in the subgroup of patients estimated to be in ≥F2 according to their FibroScan score.
1.3 Scenario using transient elastography (FibroScan)
Transient elastography is the most widely available and validated non-invasive test to assess the level of fibrosis in patients with advanced liver disease and is recommended by both the American Association for the Study of Liver Diseases (AASLD) and EASL (4, 7). EASL clinical practice guidelines on non-invasive tests for the evaluation of liver disease severity and prognosis stipulate that the diagnostic accuracy of transient elastography for detecting significant fibrosis in patients with advanced liver disease is good, with diagnostic accuracy (area under the receiver operating characteristic curve [AUROC]) around 0.85 (4). Similar AUROCs were detected in meta-analyses describing the diagnostic accuracy of transient elastography for predicting liver fibrosis in patients with CHB. Meta-analyses of studies comprising CHB patients define an optimal cut-off value of transient elastography for diagnosing METAVIR stage ≥F2 as 7.2 kPa (5, 6). However, differences in the cut-off value for METAVIR stage ≥F2 were present in the studies analysed in the meta-analyses, supporting claims by clinical experts that there is some heterogeneity regarding the appropriate cut-off values.
As a result, we have explored three subgroup analyses based on combining response at Week 24 and 48 by METAVIR Score (≥F2) with two published corresponding baseline liver stiffness measures (FibroScan ≥8.0kPA and FibroScan ≥7.25 kPA) (4, 6). As no extrapolations could be carried out for the subgroups in time for this response, the extrapolations are derived using the odds ratios of response rates between the extrapolated and observed data in the overall population. The results of these analyses are presented in * Note that [redacted] of patients had missing data for METAVIR fibrosis score at baseline, hence the much smaller sample size.

Table 4 to Table 6 below.

Table 2: Results of the subgroup analyses for virologic response
<table>
<tr><th></th><th>Bulevirtide 2 mg
(n=49)</th><th>Delayed treatment
(n=51)</th></tr>
<tr><td colspan="3">Overall population</td></tr>
<tr><td>n</td><td>49</td><td>51</td></tr>
<tr><td>Proportion of responders at Week</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
</td><td></td></tr>
</table>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment

24, n (%)		
Proportion of responders at Week 48, n (%)	[redacted]	[redacted]
Difference at Week 48	[redacted]	
METAVIR stage ≥F2* subgroup		
n	[redacted]	[redacted]
Proportion of responders at Week 24, n (%)	[redacted]	[redacted]
Proportion of responders at Week 48, n (%)	[redacted]	[redacted]
Difference at Week 48	[redacted]	
FibroScan score ≥7.25 kPa subgroup (TE cut-off based on Qi *et al.,* 2018)		
n	[redacted]	[redacted]
Proportion of responders at Week 24, n (%)	[redacted]	[redacted]
Proportion of responders at Week 48, n (%)	[redacted]	[redacted]
Difference at Week 48	[redacted]	
FibroScan score ≥8.0 kPa subgroup (TE cut-off based on EASL, 2021)		
n	[redacted]	[redacted]
Proportion of responders at Week 24, n (%)	[redacted]	[redacted]
Proportion of responders at Week 48, n (%)	[redacted]	[redacted]
Difference at Week 48	[redacted]	

* Note that [redacted] of patients had missing data for METAVIR fibrosis score at baseline, hence the much smaller sample size. TE = transient elastography (e.g., FibroScan).

Table 3: Results of the subgroup analyses for combined response

	Bulevirtide 2 mg (n=49)	**Delayed treatment (n=51)**
Overall population		
n	**49**	**51**
Proportion of responders at Week 24, n (%)	[redacted]	[redacted]

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment

Proportion of responders at Week 48, n (%)	[redacted]	[redacted]
Difference at Week 48	[redacted]	
METAVIR stage ≥F2* subgroup		
n	[redacted]	[redacted]
Proportion of responders at Week 24, n (%)	[redacted]	[redacted]
Proportion of responders at Week 48, n (%)	[redacted]	[redacted]
Difference at Week 48	[redacted]	
FibroScan score ≥7.25 kPa subgroup		
n	[redacted]	[redacted]
Proportion of responders at Week 24, n (%)	[redacted]	[redacted]
Proportion of responders at Week 48, n (%)	[redacted]	[redacted]
Difference at Week 48	[redacted]	
FibroScan score ≥8.0 kPa subgroup		
n	[redacted]	[redacted]
Proportion of responders at Week 24, n (%)	[redacted]	[redacted]
Proportion of responders at Week 48, n (%)	[redacted]	[redacted]
Difference at Week 48	[redacted]	

* Note that [redacted] of patients had missing data for METAVIR fibrosis score at baseline, hence the much smaller sample size.

Table 4: Scenario applying responses from METAVIR score ≥F2

Analysis	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	Base-case ICER (£/QALY)
Company	[redacted]	6.31	[redacted]	£29,982	£32,437
Company with severity modifier				£24,985	£27,031
EAG	[redacted]	4.43	[redacted]	£44,326	£47,876
EAG with severity modifier				£36,938	£39,897

Note: we were unable to set the model to the EAG base case of £48,097 reported in the appraisal consultation document. The EAG base case ICERs therefore represent the closest result we were able to obtain. The Company's

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>updated base-case ICERs reflect the assumptions detailed on page 11.

Table 5: Scenario applying responses from FibroScan score ≥7.25 kPA

<table>
<tr><th>Analysis</th><th>Incremental costs (£)</th><th>Incremental LYG</th><th>Incremental QALYs</th><th>ICER incremental (£/QALY)</th><th>Base-case ICER (£/QALY)</th></tr>
<tr><td>Company</td><td>[redacted]</td><td>4.79</td><td>[redacted]</td><td>£32,754</td><td>£32,437</td></tr>
<tr><td colspan="4">Company with severity modifier</td><td>£27,295</td><td>£27,031</td></tr>
<tr><td>EAG</td><td>[redacted]</td><td>3.37</td><td>[redacted]</td><td>£48,325</td><td>£47,876</td></tr>
<tr><td colspan="4">EAG with severity modifier</td><td>£40,271</td><td>£39,897</td></tr>
</table>
Note: we were unable to set the model to the EAG base case of £48,097 reported in the appraisal consultation document. The EAG base case ICERs therefore represent the closest result we were able to obtain. The Company's updated base-case ICERs reflect the assumptions detailed on page 11.

Table 6: Scenario responses from FibroScan score ≥8.0 kPA

<table>
<tr><th>Analysis</th><th>Incremental costs (£)</th><th>Incremental LYG</th><th>Incremental QALYs</th><th>ICER incremental (£/QALY)</th><th>Base-case ICER (£/QALY)</th></tr>
<tr><td>Company</td><td>[redacted]</td><td>4.80</td><td>[redacted]</td><td>£32,705</td><td>£32,437</td></tr>
<tr><td colspan="4">Company with severity modifier</td><td>£27,254</td><td>£27,031</td></tr>
<tr><td>EAG</td><td>[redacted]</td><td>3.37</td><td>[redacted]</td><td>£48,273</td><td>£47,876</td></tr>
<tr><td colspan="4">EAG with severity modifier</td><td>£40,227</td><td>£39,897</td></tr>
</table>
Note: we were unable to set the model to the EAG base case of £48,097 reported in the appraisal consultation document. The EAG base case ICERs therefore represent the closest result we were able to obtain. The Company's updated base-case ICERs reflect the assumptions detailed on page 11.</td><td></td></tr>
<tr><td></td><td>Company</td><td>Gilead</td><td>Topic 2 The mean age and cirrhosis status of people diagnosed with hepatitis D in the UK

ACD section 3.7 "People in Spaan et al. had a baseline age of 35 years and 60% had cirrhosis. In MYR 301 the baseline age was 42 years and 47% had cirrhosis... The company also presented data published by Public Health England (now the UK Health Security Agency [UKHSA]) on routine blood-borne virus testing. The median age between 2011 to 2020 was around 36 years
ACD section 3.16 "The committee noted that it would like to see the mean age and cirrhosis status of UK patients at diagnosis based on UKHSA data"

Company response:
• The mean age of people diagnosed with hepatitis D in the UK determined by UKHSA does not alter the eligibility for a severity weight when applied to the company base-case.
• A significant proportion of patients with hepatitis D are young, and the inability to apply a severity modifier</td><td>Comment noted. Thank you. The committee discussed this further at the second committee meeting. Its discussions and conclusions are reported in sections 3.9 and 3.10 of the final draft guidance.</td></tr>
</table>

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>
due to a fraction of patients being older is discriminatory towards this patient population with a large unmet need.

2.1 Summary

In the absence of UK clinical study sites in the pivotal MYR 301 clinical study, the Company felt it was most appropriate to use baseline characteristics from Spaan et al. (2020), a retrospective analysis of 107 patients with CHD in the UK (4), in the economic model. Data on the median age of patients with CHD, collected by UKHSA from 2011 to 2020, was also presented to the committee, however the committee considered that UKHSA data on mean (rather than median) age at baseline would be more helpful to increase certainty in the cost-effectiveness results and the severity weighting applied to bulevirtide, despite the age distribution being skewed to the left e.g., the majority of patients being young.
UKHSA confirmed that the median age was 35.0 years (n=602 patients) for patients when HDV ribonucleic acid (RNA) was first detected with a mean age 37.4 ± 10.6 years. When considering the cohort of patients who are currently alive, the median age remained at 35.0 years (n=570 patients) with the mean age for patients when HDV RNA was first detected decreased to 36.9 ± 10.2 years (5). This data supports the Company's base case analysis which assumed an average age of 35.0 years as per Spaan et al. (2020) (4). The data on mean age of patients with CHD at baseline in the UK supplied by UKHSA has a minor impact on the ICER (see Table 7 below) and does not alter the eligibility for a severity weighting of 1.2 when applied to the Company base-case.
UKHSA data on baseline age at diagnosis implies that the majority of CHD patients in the UK are young, approx. 55% being age 36.49 years or younger which corresponds to the threshold for the severity modifier in the EAG's model. The Company is therefore of the opinion that the severity modifier should be applied. The Committee noted in the draft guidance the high disease burden of chronic hepatitis D, therefore we believe it would be unreasonable to characterise CHD as a non-severe condition. Failing to apply a severity weighting as a result of a fraction of patients being older is potentially discriminatory towards the large cohort (55%) of young patients diagnosed with hepatitis D who have a large unmet need.

2.2 Scenario based on mean age from UKHSA

The committee considered basing the baseline age for patients with cirrhosis on diagnosis in the UK with CHD on UKHSA data. Data on cirrhosis status were not provided by UKHSA however the mean age of all patients when they first tested positive for HDV RNA has been explored in the model by changing the baseline age to 37.4 years. Results are reported in Table 7.
Table 7: Cost-effectiveness results of scenario where baseline age is set to mean of 37.4 years

<table>
<tr><th>Analysis</th><th>Incremental costs (£)</th><th>Incremental LYG</th><th>Incremental QALYs</th><th>ICER incremental (£/QALY)</th><th>Base-case ICER (£/QALY)</th></tr>
<tr><td>Company</td><td>[redacted]</td><td>4.78</td><td>[redacted]</td><td>£32,943</td><td>£32,437</td></tr>
<tr><td colspan="4">Company with severity modifier</td><td>£27,452</td><td>£27,031</td></tr>
<tr><td>EAG</td><td>[redacted]</td><td>3.69</td><td>[redacted]</td><td>£46,004</td><td>£47,876</td></tr>
<tr><td colspan="4">EAG with severity modifier</td><td>£38,337</td><td>£39,897</td></tr>
</table>
</td><td></td></tr>
</table>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Note: we were unable to set the model to the EAG base case of £48,097 reported in the appraisal consultation document. The EAG base case ICERs therefore represent the closest result we were able to obtain. **Topic 3 Model progression/regression rates** **ACD section 3.9** *"Clinical experts agreed with the company that combined responders would have a low risk of progression through fibrosis stages, but argued that this would not be zero because this group could still have detectable levels of virus. They added that even combined responders may still be at risk of hepatocellular carcinoma. Clinical experts further explained that it is plausible that fibrosis regression could occur in combined responders, but added that the company's assumed transition probabilities for fibrosis regression seemed high."* **Company response:** • Including a small but non-zero risk of progression for combined responders in the model had a minor impact on the company's base case ICER. • Reducing regression rates in the model had a more substantial impact, but given these rates of regression were informed by real-world evidence in patients with viral hepatitis, we do not consider the requested scenario analysis to be realistic. **3.1 Summary** Data from MYR 301 are currently too immature to reliably inform the impact of bulevirtide on rate of progression. However, it is reasonable to assume that a patient who has had a ≥99% (≥2-$\log_{10}$) reduction in their viral RNA load and alanine aminostransferase (ALT) normalisation will have a substantial benefit approaching zero progression if their hepatitis B infection is well controlled. However, we have carried out scenario analyses in the following sections that demonstrate that assuming a low rate of progression *relative to* virologic-only responders has a low impact on the ICER compared with the Company base case. Similarly, the estimates for regression in the model were based on the published literature in viral hepatitis. The source informing regression from the compensated cirrhosis (CC) (F4) to F3 health states was Farci *et al.,* (2004) (8), a longitudinal study of 41 CHD patients based in Italy. Thirty-six patients with CHD who participated in a randomised controlled trial of a 48-week course of high (9 million units) or low (3 million units) doses of PEG-IFN or no treatment were followed for an additional 2 to 14 years. The mean follow-up time was 10.8 years. The regression rates in the model were informed by the regression rates observed in patients who had sustained biochemical response in Farci *et al.,* (2004). For F3 to F2, regression rates were sourced from Marcellin *et al.,* (2013) (9), a 5-year follow-up study of HBV mono-infected patients who had been enrolled in a 48-week randomised clinical trial where they had been treated with tenofovir disoproxil fumarate (TDF) or adefovir dipivoxil. In the follow-up study, patients received treatment with TDF. Six hundred and forty-one patients were recruited from 80 different study locations including the US, Canada, France, Turkey and the UK. Five hundred and eighty-five (91%) of these patients entered the open-label phase (follow-up study) and 489 patients (76%) completed 240 weeks of the study. Regression rates in the model were informed by the proportion of patients who experienced viral suppression while on treatment with TDF.	Comment noted. Thank you. The committee discussed this further at the second committee meeting. Its discussions and conclusions are reported in sections 3.12 and 3.13 of the final draft guidance.

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>
These rates of regression are likely generalisable to a patient with CHD experiencing a combined response. We have nevertheless, as per the committee's request, carried out a scenario analysis where regression rates in the model are reduced. While this has a larger magnitude of impact on the ICER than reducing progression rates, we do not consider this to be a realistic scenario given that our original modelled estimates are obtained from real-world evidence of regression in viral hepatitis.
3.2 Progression through fibrosis stage for combined responders

The committee considered that the risk of progression through fibrosis stage for the combined responders should be low but not zero. We have explored this by assuming that progression is reduced relative to that of partial responders instead of assuming that it is zero. We have carried out an analysis where we assume that the hazard ratio for progression in combined responders is 20% of that applied to partial responders. That is, 0.08 in combined responders vs. 0.42 in partial responders for fibrosis states Fx->Fx+1 and 0.05 in combined responders vs. 0.26 in partial responders for fibrosis states F4->decompensated cirrhosis (DCC). Results are reported in Error! Reference source not found..

Table 8: Scenario of progression through fibrosis stage for combined responders

<table>
<tr><th>Analysis</th><th>Incremental costs (£)</th><th>Incremental LYG</th><th>Incremental QALYs</th><th>ICER incremental (£/QALY)</th><th>Base-case ICER (£/QALY)</th></tr>
<tr><td>Company</td><td>[redacted]</td><td>4.74</td><td>[redacted]</td><td>£33,053</td><td>£32,437</td></tr>
<tr><td colspan="4">Company with severity modifier</td><td>£27,544</td><td>£27,031</td></tr>
<tr><td>EAG</td><td>[redacted]</td><td>3.32</td><td>[redacted]</td><td>£49,014</td><td>£47,876</td></tr>
<tr><td colspan="4">EAG with severity modifier</td><td>£40,845</td><td>£39,897</td></tr>
</table>
Note: we were unable to set the model to the EAG base case of £48,097 reported in the appraisal consultation document. The EAG base case ICERs therefore represent the closest result we were able to obtain.

3.3 Progression to hepatocellular carcinoma for combined responders

The committee considered that the risk of progression to hepatocellular carcinoma (HCC) for combined responders should be low but not zero. We have explored this by assuming that progression is reduced relative to that of partial responders instead of assuming that it is zero. We have carried out an analysis where we assume that the hazard ratio for progression in combined responders is 20% of that applied to partial responders. That is, 0.07 in complete responders vs. 0.34 in partial responders for all transitions to HCC. Results are reported in Error! Reference source not found..
Table 9: Scenario of progression to hepatocellular carcinoma for combined responders

<table>
<tr><th>Analysis</th><th>Incremental costs (£)</th><th>Incremental LYG</th><th>Incremental QALYs</th><th>ICER incremental (£/QALY)</th><th>Base-case ICER (£/QALY)</th></tr>
<tr><td>Company</td><td>[redacted]</td><td>4.71</td><td>[redacted]</td><td>£33,055</td><td>£32,437</td></tr>
<tr><td colspan="4">Company with severity modifier</td><td>£27,546</td><td>£27,031</td></tr>
<tr><td>EAG</td><td>[redacted]</td><td>3.76</td><td>[redacted]</td><td>£45,711</td><td>£47,876</td></tr>
</table>
</td><td></td></tr>
</table>

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td>EAG with severity modifier</td><td>£38,092</td><td>£39,897</td></tr>
</table>
Note: we were unable to set the model to the EAG base case of £48,097 reported in the appraisal consultation document. The EAG base case ICERs therefore represent the closest result we were able to obtain.

3.4 Regression in combined responders

The committee considered that the Company’s assumed transition probabilities for fibrosis regression appeared high. We have explored this by carrying out an analysis where we reduced the probability of fibrosis regression for combined responders by 50% (4.41% for CC (F4) → F3; and 6.65% for F3 → F2 in the scenario). Results are reported in Error! Reference source not found.. It can be seen that the impact on the Company’s base case ICER is modest, resulting in an increase of £907 however the ICER remains well below the a ICER threshold of £30,000 per QALY gained.
Table 10: Scenario of regression in combined responders
<table>
<tr><th>Analysis</th><th>Incremental costs (£)</th><th>Incremental LYG</th><th>Incremental QALYs</th><th>ICER incremental (£/QALY)</th><th>Base-case ICER (£/QALY)</th></tr>
<tr><td>Company</td><td>[redacted]</td><td>4.64</td><td>[redacted]</td><td>£33,526</td><td>£32,437</td></tr>
<tr><td>Company with severity modifier</td><td></td><td></td><td></td><td>£27,938</td><td>£27,031</td></tr>
<tr><td>EAG</td><td>[redacted]</td><td>3.15</td><td>[redacted]</td><td>£50,697</td><td>£47,876</td></tr>
<tr><td>EAG with severity modifier</td><td></td><td></td><td></td><td>£42,247</td><td>£39,897</td></tr>
</table>
Note: we were unable to set the model to the EAG base case of £48,097 reported in the appraisal consultation document. The EAG base case ICERs therefore represent the closest result we were able to obtain.
</td><td></td></tr>
<tr><td></td><td>Company</td><td>Gilead</td><td>
Topic 4 Treatment duration beyond 48 weeks in MYR 301

ACD section 3.11 “Clinical experts broadly agreed with the company’s model assumptions for combined responders and non-responders but were less sure of what would happen for virological responders…Clinical experts added that treatment would also likely continue for combined or virological responders who develop hepatocellular carcinoma, and that for people with convincing evidence of virus eradication, treatment would likely be stopped.
The committee agreed with the clinical experts’ assumptions but noted that there is remaining uncertainty around whether the stopping rules assumed by the company are aligned with those used in MYR 301 until data beyond 48 weeks becomes available”

Company response:
• The Company has carried out a scenario analyses which explores the impact of continuing treatment in patients who develop HCC and relaxing the treatment continuation criteria to achievement of virologic response only.
• While assuming the same continuation rules for virologic and combined responders increases the ICER,
</td><td>Comment noted. Thank you. The committee discussed this further at the second committee meeting. Its discussions and conclusions are reported in sections 3.14, 3.15, 3.16 and 3.17 of the final draft guidance.</td></tr>
</table>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			we note that clinicians were unsure that virologic responders would have the same continuation rules and that this may only apply to specific cases. • The more realistic scenario that patients with virus eradication could discontinue treatment substantially offsets any effect from a minority of virologic responders continuing treatment. **4.1 Summary** The Company has included a range of scenarios to explore how treatment continuation criteria impact on estimates of cost-effectiveness. These include: • Continuing treatment with bulevirtide in patients who develop HCC. • Assuming the same continuation rules for virologic responders as combined responders, either at Week 48 or Week 72. • Assuming that patients with undetectable HDV RNA discontinue bulevirtide. Continued treatment for HCC patients is a scenario previously explored by the EAG and included in their base case, with negligible impact on the ICER. With respect to the scenarios applying the same continuation rules for virologic-only responders, we note from the ACD that clinicians appeared unsure about this assumption, and that it might apply only in specific circumstances e.g., "*if a patient had a virological response but high ALT for reasons other than hepatitis, for example fatty liver disease or alcohol use*." We therefore consider that the results of this scenario analysis represent a situation where all patients with a virological response remain on treatment. Finally, the scenario where patients with undetectable HDV RNA discontinue treatment is a realistic one given this approach is taken for other viral hepatitis treatments. In isolation, this scenario leads to a substantial reduction in the ICER as can be seen in Table 14. Applying this clinically realistic scenario to the more unrealistic scenario that *all* virologic-only responders continue treatment substantially reduces the unfavourable impact of the latter assumption. **4.2 Treatment continuation with hepatocellular carcinoma** The committee considered that treatment should be continued for people who develop HCC. We have explored this by carrying out an analysis where we captured the cost of treatment for HCC patients in the model. Note that this was a scenario that had already previously been introduced by the EAG to which the model is insensitive. Furthermore, the Company has now adopted this as part of their new base case. For information purposes, we compare the results with the original Company base ICER of £33,134 (£27,612 with severity modifier of 1.2). Results are reported in Table 11, noting that the EAG base case does not change given this assumption is already included. **Table 11: Scenario of treatment continuation with HCC** **Analysis** | **Incremental** | **Incremental** | **Incremental** | **ICER incremental** | **Base-case**	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment

	costs (£)	LYG	QALYs	(£/QALY)	ICER (£/QALY)
Company	[redacted]	4.91	[redacted]	£32,437	£33,134[1]
Company with severity modifier				£27,031	£27,612[1]
EAG	[redacted]	3.45	[redacted]	£47,876	£47,876
EAG with severity modifier				£39,897	£39,897

[1]These represent the original post-technical engagement base case ICERs presented at committee.

Note: we were unable to set the model to the EAG base case of £48,097 reported in the appraisal consultation document. The EAG base case ICERs therefore represent the closest result we were able to obtain.

4.3 Treatment continuation for virologic responders

The committee considered having the same treatment continuation assumptions for virologic responders as for combined responders. We have explored this in the model by changing the response criteria in the existing model Settings sheet. That is, at Week 48 non-responders discontinue treatment but virologic responders remain on treatment without any further assessment at Week 72. We then carry out a further scenario where the assessment for non-response is instead carried out at Week 72 instead of Week 48 (which uses the model extrapolations in the Company's scenario). Results are reported in
Table 12 and Table 13.
This scenario leads to the largest increase in the ICER, but we note that the committee also discussed the potential for patients with virus eradication to discontinue treatment, modelled in the next scenario. We also explore the impact of combining the present scenario with that of discontinuation of treatment with virus eradication.

Table 12: Scenario with treatment continuation for virologic responders (Week 48)

Analysis	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	Base-case ICER (£/QALY)
Company	[redacted]	3.66	[redacted]	£38,964	£32,437
Company with severity modifier				£32,470	£27,031
EAG	[redacted]	3.18	[redacted]	£55,135	£47,876
EAG with severity modifier				£45,946	£39,897

Table 13: Scenario with treatment continuation for virologic responders (Week 72)

Analysis	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	Base-case ICER (£/QALY)
Company	[redacted]	3.66	[redacted]	£39,466	£32,437
Company with severity modifier				£32,889	£27,031
EAG	[redacted]	3.18	[redacted]	£55,718	£36,749
EAG with severity modifier				£46,432	£39,897

Note: we were unable to set the model to the EAG base case of £48,097 reported in the appraisal consultation

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>
document. The EAG base case ICERs therefore represent the closest result we were able to obtain.

4.4 Stopping treatment with virus eradication

The committee considered having the treatment stopped for those with convincing evidence of virus eradication. In the absence of specific feedback from clinicians regarding what constitutes “convincing evidence”, we have explored this by assuming that patients with a combined response who had undetectable HDV RNA at 48 weeks discontinue treatment 52 weeks later. This is achieved by removing the costs of bulevirtide from Week 120 onward for the proportion of combined response patients with undetectable HDV RNA at 48 weeks ([redacted]) while maintaining them in the complete response health states. Note that this will still overpredict costs given that, for simplicity, we do not remove the costs of hepatitis D monitoring. The results of this scenario are presented in Table 14. As this has now been adopted as the Company’s new base case, we present the results compared with our original Company base case ICER of £33,134 (£27,612 with severity modifier of 1.2).
Table 14: Scenario of stopping treatment with virus eradication
<table>
<tr><th>Analysis</th><th>Incremental costs (£)</th><th>Incremental LYG</th><th>Incremental QALYs</th><th>ICER incremental (£/QALY)</th><th>Base-case ICER (£/QALY)</th></tr>
<tr><td>Company</td><td>[redacted]</td><td>4.91</td><td>[redacted]</td><td>£32,437</td><td>£33,134[1]</td></tr>
<tr><td colspan="4">Company with severity modifier</td><td>£27,031</td><td>£27,612[1]</td></tr>
<tr><td>EAG</td><td>[redacted]</td><td>3.45</td><td>[redacted]</td><td>£42,413</td><td>£47,876</td></tr>
<tr><td colspan="4">EAG with severity modifier</td><td>£35,344</td><td>£39,897</td></tr>
</table>
[1]These represent the original post-technical engagement base case ICERs presented at committee.

Note: we were unable to set the model to the EAG base case of £48,097 reported in the appraisal consultation document. The EAG base case ICERs therefore represent the closest result we were able to obtain.

4.5 Treatment continuation for virologic responders combined with stopping treatment with virus eradication

In section 4.3 we explored changing the response criteria to virologic. That is, at Week 48 non-responders discontinue treatment but virologic responders remain on treatment without any further assessment at Week 72. Below we combine that scenario with that in section 4.4 where patients with virus eradication are assumed to discontinue treatment with bulevirtide. As previously, we deduct the costs of bulevirtide from Week 120 onward for the proportion of patients with undetectable HDV RNA at 48 weeks while maintaining them in the complete response health states (now assumed within our Company base case). In this scenario, the proportion of patients with undetectable RNA is [redacted], as the definition of a complete responder is virologic whereas in section 4.4 it was combined response. The results of this scenario are presented in Table 15.
Table 15: Scenario of treatment continuation for virologic responders combined with stopping treatment with
</td><td></td></tr>
</table>

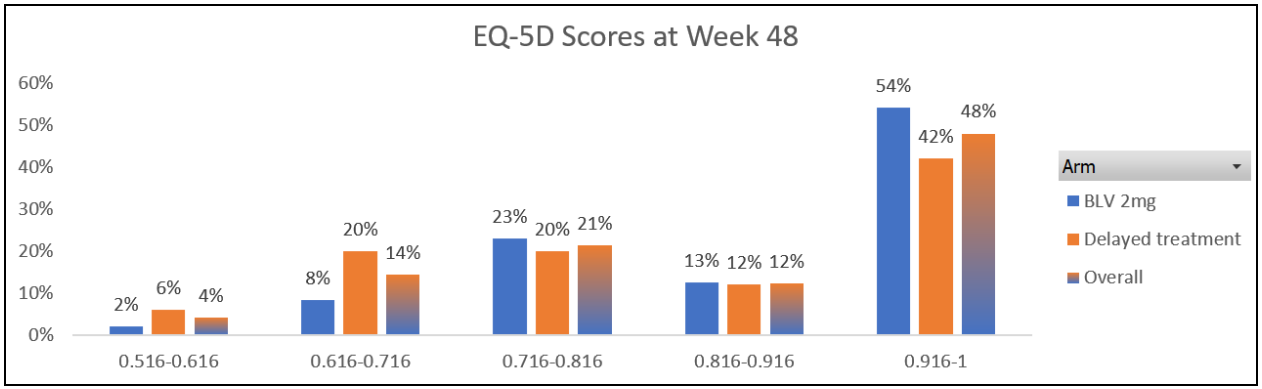
<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>
virus eradication
<table>
<tr><th>Analysis</th><th>Incremental costs (£)</th><th>Incremental LYG</th><th>Incremental QALYs</th><th>ICER incremental (£/QALY)</th><th>Base-case ICER (£/QALY)</th></tr>
<tr><td>Company</td><td>[redacted]</td><td>3.66</td><td>[redacted]</td><td>£39,466</td><td>£32,437</td></tr>
<tr><td colspan="4">Company with severity modifier</td><td>£32,889</td><td>£27,031</td></tr>
<tr><td>EAG</td><td>[redacted]</td><td>3.18</td><td>[redacted]</td><td>£47,909</td><td>£47,876</td></tr>
<tr><td colspan="4">EAG with severity modifier</td><td>£39,924</td><td>£39,897</td></tr>
</table>
Note: we were unable to set the model to the EAG base case of £48,097 reported in the appraisal consultation document. The EAG base case ICERs therefore represent the closest result we were able to obtain.
</td><td></td></tr>
<tr><td></td><td>Company</td><td>Gilead</td><td>
Topic 5 The size of the utility gain for combined responders

ACD section 3.12 “The committee was less certain about the size of the utility gain that should be applied. It noted the lack of justification for the Tobit approach and highlighted that the resulting utility gain from the regression model was not statistically significant. It recalled that in previous appraisals of hepatitis C, combined response was associated with a smaller utility gain than assumed by the company. The committee concluded that the size of the utility benefit for combined responders was uncertain.”

Company response:
• NICE methods guidance stipulates that where possible utilities from the technology’s clinical trials should be used in the economic model. Our choice of regression model for generating utilities was underpinned by observed ceiling effects in the MYR 301 data.
• Utility gain for patients with sustained virologic response (SVR) in other hepatitis appraisals has been slightly lower (different by ≤0.02) than that observed for combined responders in MYR 301, however this may be explained by differences in the type of hepatitis infection and population.

5.1 Summary

The committee queried the method used for deriving the utility gain of responders from the MYR 301 data and requested a comparison with the utility values used in other relevant technology appraisals (TAs). In section 5.2 we provide more information regarding the observed ceiling effect that justifies the use of the Tobit regression model. In section 5.3 we present the results of a literature search covering both prior NICE TAs and the published literature. The results of this search showed high heterogeneity, highlighting that utility gain can vary significantly by population sampled. The values used for SVR in other NICE TAs were broadly in line with those obtained from MYR 301 using our Tobit regression model. However, NICE methods stipulate that the preferred source of utility in an economic model is to use “EQ-5D reported by patients/carers in a relevant study” (10). As the MYR 301 study is the only study that reports utility gain from the relevant population of CHD patients, then the data from MYR 301 are the appropriate values to be used in the model.
</td><td>Comment noted. Thank you. The committee discussed this further at the second committee meeting. Its discussions and conclusions are reported in sections 3.18 and 3.19 of the final draft guidance.</td></tr>
</table>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Notwithstanding this, we have explored in section 5.4 the impact of utility gain in a scenario analysis by assuming 50% or 75% of the current utility gain for responders. Results for both cases are reported in Table 18 and Table 19, in which it can be seen that this has a modest impact on the Company's base case cost-effectiveness results. **5.2 Justification for use of the Company's Tobit model for utility gain** The committee noted the lack of justification for the Company's Tobit model around median (CLAD [censored least absolute deviations] regression) approach to deriving utility gain for responders. EuroQol 5 Dimension (EQ-5D) index scores from MYR 301 are presented in Figure 1, which show that the distribution of the EQ-5D index was significantly skewed to the left, with the peak of the histogram on the right; approximately 40-50% of the subjects obtaining the highest score. This strongly suggests that a ceiling effect was present in the data, which occurs when a high proportions of subjects in a study have maximum scores on the observed variables. **Figure 1: EQ-5D scores at Week 48 overall and treatment by arm**  When data have pronounced ceiling effects, the use of ordinary least squares (OLS) regression violates the statistical requirement for linearity of conditional expectation, leading to inaccurate predictions of preference-based scores and inaccurate identification of predictor variables (11). The Tobit model is preferable over OLS regression when a ceiling effect is present or the dependent variable is censored. The CLAD approach is based on an assumption that the median will be more robust to ceiling effects than the mean. The coefficients are estimated so as to minimize the sum of the absolute deviations from the regression line (12, 13). The Company therefore considered that the Tobit CLAD regression comprised the most appropriate approach to deriving utility gain of responders from the MYR 301 data. **5.3 Utility gain for responders from past technology appraisals** The committee considered having alternative estimates of utility gain for combined responders, based on previous hepatitis technology appraisals (TAs). The Company has explored this issue by reviewing previous TAs in hepatitis B and C, supplemented with data from the literature by re-examining the papers retried in our health-related quality of life systematic literature review. In hepatitis B TAs, no utility gain was assumed for virologic responders who were not in SVR and patients with SVR were assumed to have a small utility decrement (1%) relative to the general population.	

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>
In TAs for hepatitis C we could only identify utility gains for patients with SVR. These are provided in Table 16 below. It can be seen that these utility gains ranged from 0.03 to 0.05. However, we note the committee's comment from TA413 that "where available, it prefers utility values collected from the clinical trials used to inform the effectiveness of the intervention under evaluation to those estimated from other sources." Given that the [redacted] value used in the economic model was directly from the MYR 301 trial data, it is therefore appropriate to use this value in the model as it was obtained from a hepatitis D-infected population in which combined response might not unreasonably lead to greater utility gains.
Values in the literature show high heterogeneity, ranging from 0.053 to 0.2 in various regression models (Table 17), demonstrating how much this can vary between different cohorts of patients. This variability further supports the need to utilise the utility gain from responders collected in the MYR 301 study, as it will be representative of a cohort of patients receiving treatment with bulevirtide for CHD.

Table 16: Utility gains for patients with SVR in NICE TAs
<table>
<tr><th>Technology Appraisal (TA)</th><th>Topic</th><th>Published date</th><th>Utility gained value</th><th>Source used</th></tr>
<tr><td>TA330</td><td>Sofosbuvir for treating chronic hepatitis C</td><td>2015</td><td>0.05</td><td>Wright et al., 2006 (14)</td></tr>
<tr><td>TA363</td><td>Ledipasvir–sofosbuvir for treating chronic hepatitis C</td><td>2015</td><td>0.04</td><td>Vera-Llonch et al., 2013 (15)</td></tr>
<tr><td>TA413</td><td>Elbasvir–grazoprevir for treating chronic hepatitis C</td><td>2016</td><td>0.03</td><td>European subgroup of the elbasvir–grazoprevir trials.</td></tr>
</table>
Table 17: Utility gains for patients with SVR in the literature
<table>
<tr><th>Study setting</th><th>Utility gained value</th><th>Reference</th></tr>
<tr><td>Clinical trials of sofosbuvir in patients with chronic HCV</td><td>0.043</td><td>Stepanova et al., 2014 (16)</td></tr>
<tr><td>Clinical trial of telaprevir combination therapy in chronic HCV</td><td>0.040</td><td>Vera-Llonch et al., 2013 (15)</td></tr>
<tr><td>Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation</td><td>0.060</td><td>Wright et al., 2006 (14)</td></tr>
<tr><td>Cross-sectional survey in chronic HCV patients in France</td><td>0.213</td><td>Samp et al., 2015 (17)</td></tr>
<tr><td>Prospective observational study, patients with chronic HCV</td><td>0.040</td><td>Juanbeltz et al., 2019 (18)</td></tr>
</table>
</td><td></td></tr>
</table>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment

in Spain		

5.4 Alternative scenarios for responder utility gains

The committee requested to see alternative estimates of utility gain for combined responders, based on previous hepatitis appraisals. As explained in the previous section, utility gains for patients in SVR have been in the same range as those observed for combined responders in MYR 301. However, recognizing that the patients in MYR 301 were not in SVR, we explore two scenarios where the current utility gain in the model ([redacted]) is reduced by 50% and 75% in Table 18 and Table 19 below. In both scenario analyses it can be seen that bulevirtide is associated with substantially higher QALYs compared to BSC, with the Company's base case ICER being below £30,000 per QALY gained with the severity modifier.

Table 18: Scenario of assuming 50% of the current utility gain for responders

Analysis	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	Base-case ICER (£/QALY)
Company	[redacted]	4.91	[redacted]	£33,938	£32,437
Company with severity modifier				£28,282	£27,031
EAG	[redacted]	3.45	[redacted]	£50,699	£47,876
EAG with severity modifier				£42,250	£39,897

Note: we were unable to set the model to the EAG base case of £48,097 reported in the appraisal consultation document. The EAG base case ICERs therefore represent the closest result we were able to obtain.

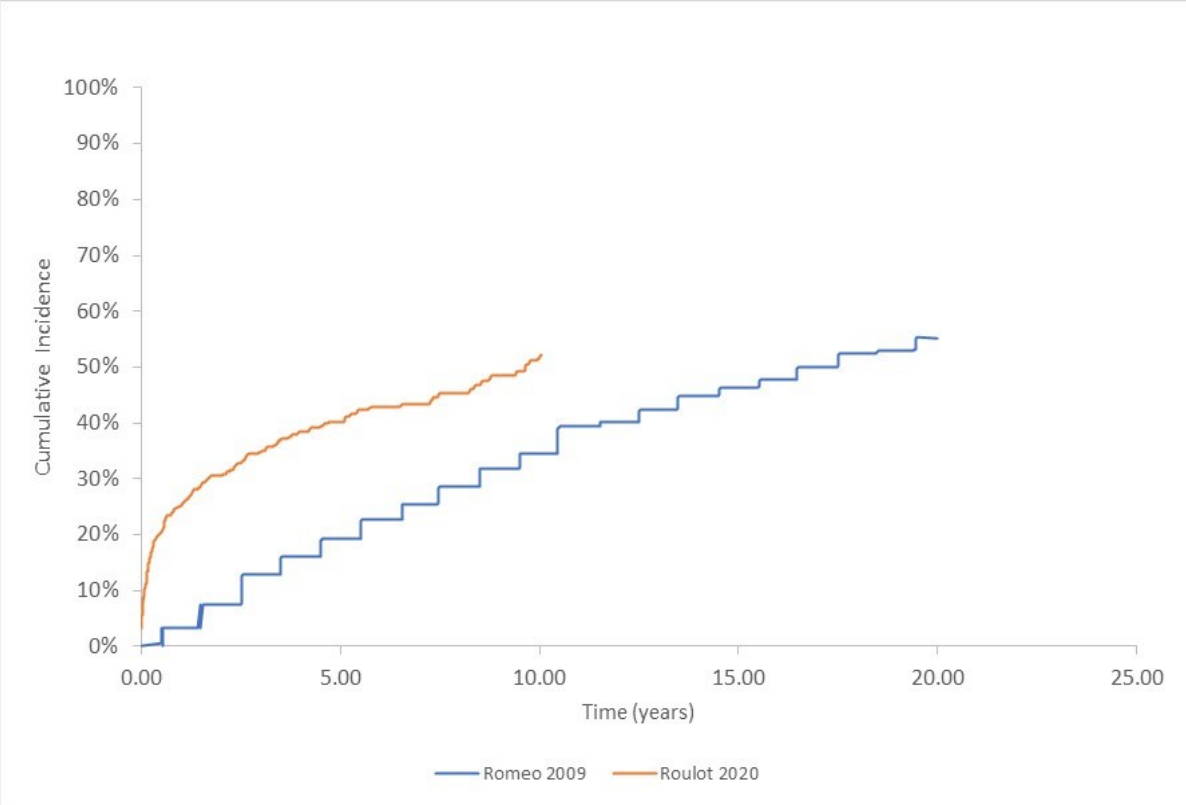
Table 19: Scenario of assuming 75% of the current utility gain for responders

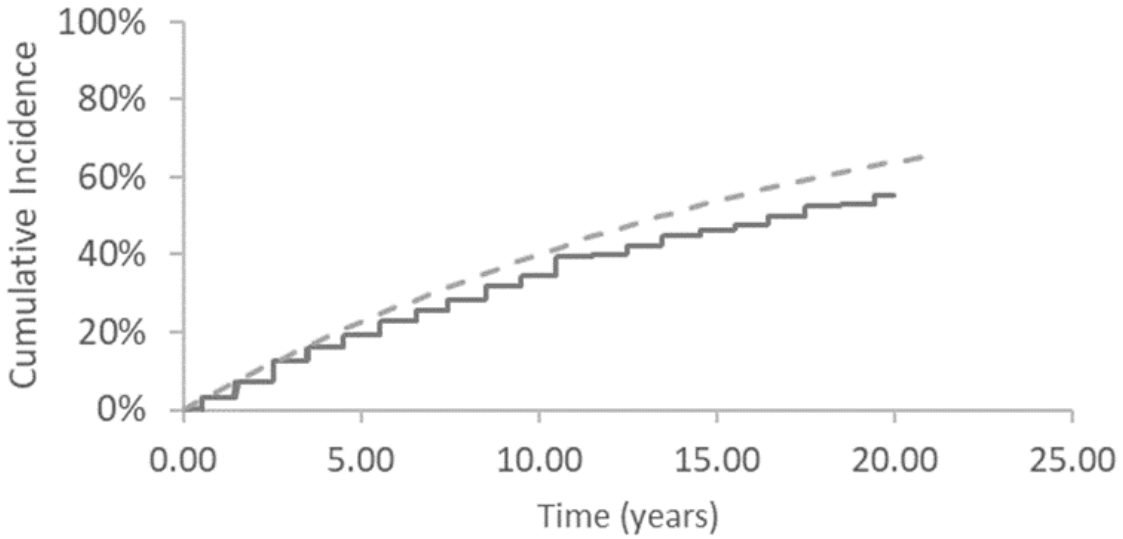
Analysis	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	Base-case ICER (£/QALY)
Company	[redacted]	4.91	[redacted]	£33,171	£32,437
Company with severity modifier				£27,642	£27,031
EAG	[redacted]	3.45	[redacted]	£49,248	£47,876
EAG with severity modifier				£41,040	£39,897

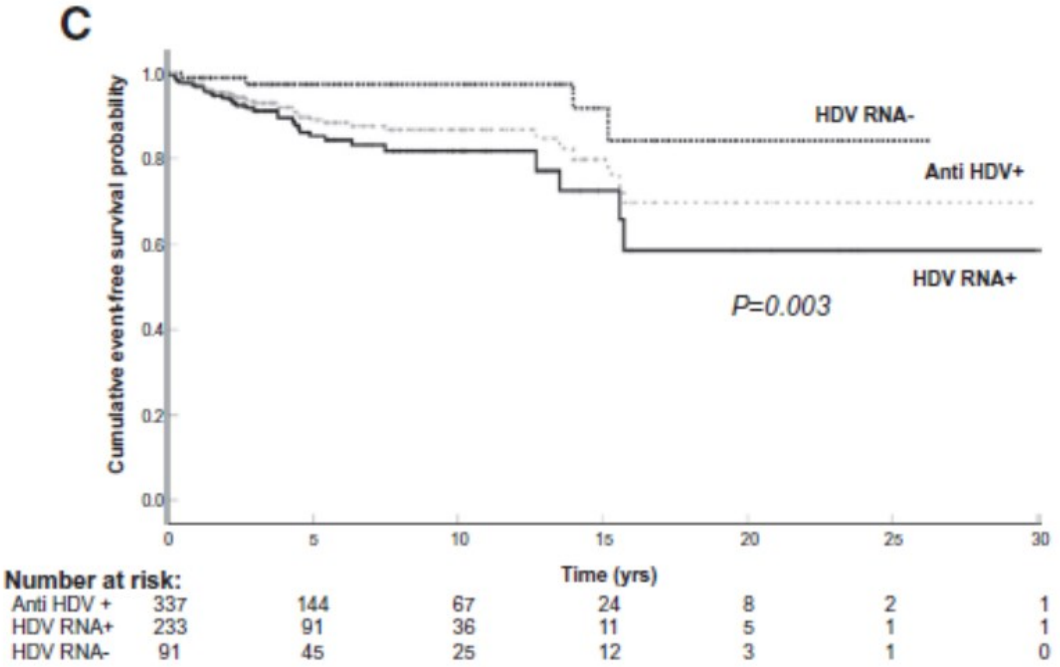
Note: we were unable to set the model to the EAG base case of £48,097 reported in the appraisal consultation document. The EAG base case ICERs therefore represent the closest result we were able to obtain.

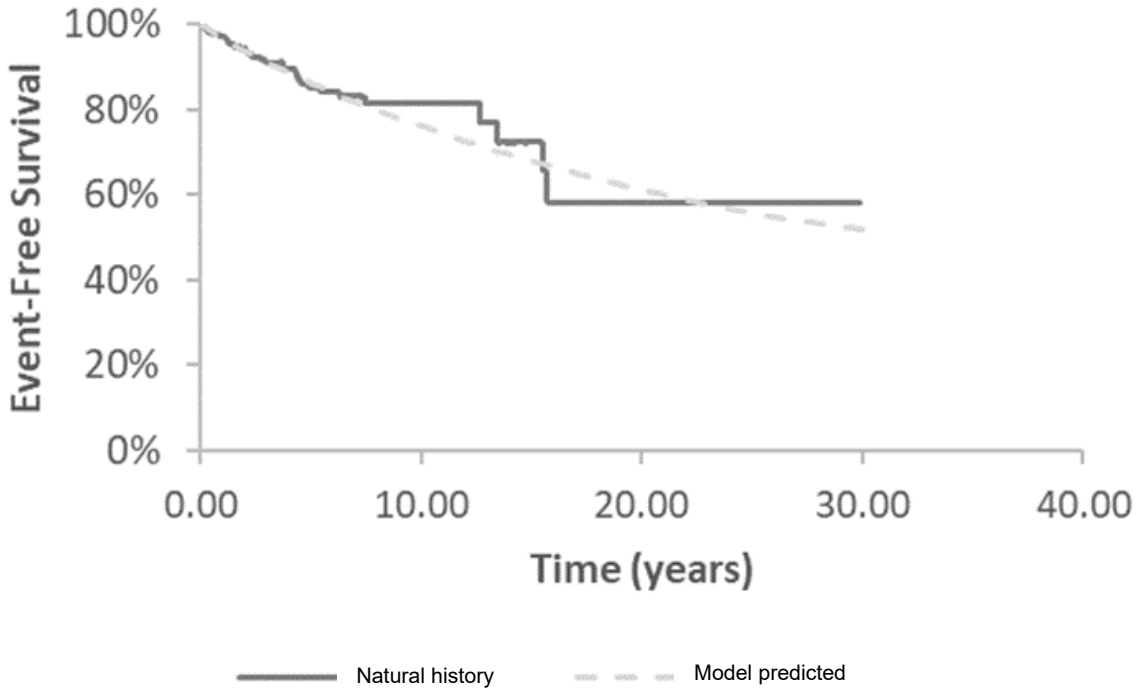
Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
	Company	Gilead	**Topic 6 The long-term survival for people on standard care, in the absence of bulevirtide** **ACD section 3.15** *"The committee added that many of the EAG's preferred assumptions around the natural history modelling of chronic hepatitis D may also affect the severity weighting calculations because they affect QALYs accrued by people having standard care…It added that validation of the model predictions for people on standard care using external literature sources would be helpful, along with graphical representations of health state occupation over time."* **Company response:** • As requested, we have validated the progression and survival rates predicted by the economic model with those in the published CHD literature by comparing Kaplan-Meier plots with survival plots extracted from the model. • There was close alignment between the model predictions and the published literature, with divergence only observed at later timepoints where costs and outcomes are discounted **6.1 Summary** The committee requested validation of the predictions of disease progression for patients on best supportive care from the economic model using the external published literature. The Company has carried this out in section **Error! Reference source not found.** for a number of model transitions, including those to more severe fibrosis states, to HCC and for overall survival. It can be seen from the superimposed Kaplan-Meier/survival plots that the model predictions align closely with those observed in the CHD literature, with the curve shapes only diverging at later timepoints. This is likely a feature of time-changing hazards of progression and death in the real-world, whereas the model uses constant transition probabilities conditional on response. Introducing time-dependent transition probabilities would require substantial reworking of the model and increase model complexity. Furthermore, in many cases divergence from the observed data only occurred after many years, by which time outcomes in the model are highly discounted and thus less likely to impact the ICER. We have furthermore, in section 6.3, produced plots of model health-state occupancy over time as well as an overall survival plot for the two arms to facilitate decision-making. **6.2 Progression/survival rates in the CHD literature** The validation of the long-term survival for people on BSC in the absence of bulevirtide was conducted based on the following factors: 1. Availability of Kaplan-Meier survival data on HDV. 2. Availability of information on granular fibrosis stages and/or data specific to compensated cirrhosis patients.	Comment noted. Thank you for providing this data to validate the natural history modelling for hepatitis D. The committee discussed this further at the second committee meeting. Its discussions and conclusions are reported in sections 3.22 amd 3.23 of the final draft guidance.

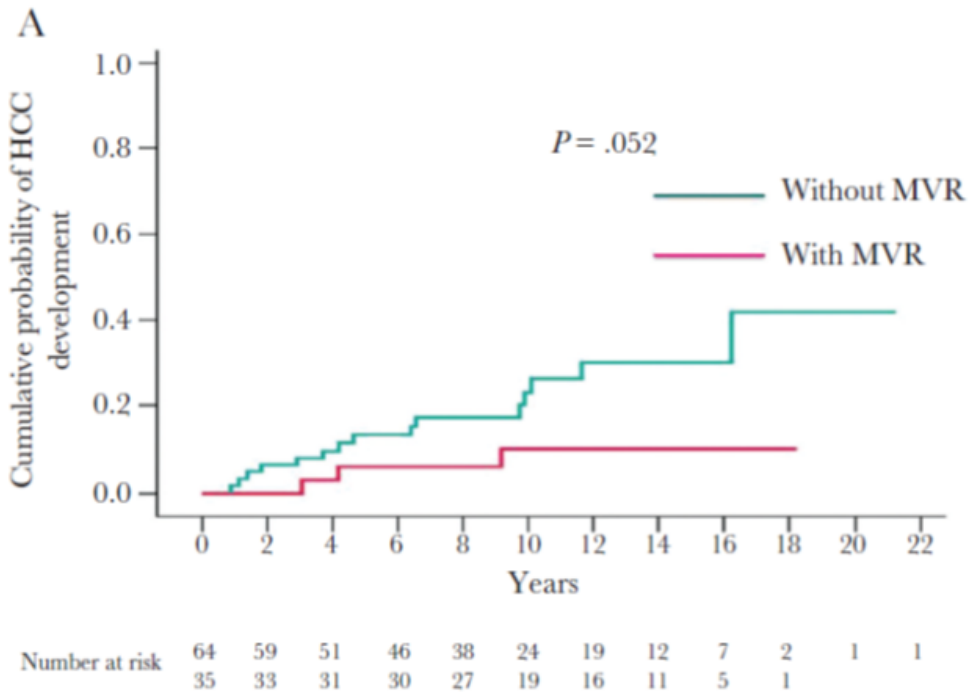
Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			3. Data specific to untreated patients or patients without treatment response (as these would be assumed to be most similar to BSC patients in the model). Kaplan-Meier curves from the selected natural history studies were digitized using the program Plot Digitizer. Baseline demographics (e.g., baseline fibrosis distribution, patient age, sex distribution) were aligned with the natural history studies based on available data. In several studies, fibrosis stage data were only available for compensated cirrhotic (F4) vs. non-cirrhotic (F0-F3) health states. In these cases, the relative distribution of patients across F0-F3 was based on Romeo *et al.,* (2009) (19). Model outcomes for advanced liver-disease events were compared against the digitized Kaplan-Meier curves from these natural history studies based on visual inspection. We have explored this in several studies, described in detail below. ***6.2.1 Compensated cirrhosis*** Given the availability of granular information regarding the distribution of patients from F0-F4 health states in the Romeo *et al.,* (2009) study, this study was selected for the validation of the economic model outcomes as compared to HDV natural history. In Romeo et al., 2009, the cumulative probability of cirrhosis at 20 years was 55% with an incidence rate of 4% per year in the overall (F0-F3) non-cirrhotic patients (Figure 1) (19). Given that the values were not reported granularly (i.e., F2-F3, F3-F4), individual transition probabilities could not be derived. Notably, these estimates from Romeo *et al.,* (2009) may even be conservative, as the Roulot *et al.,* (2020) study of a French retrospective cohort of HDV patients estimated a 5-year risk of cirrhosis of 49.4% in non-cirrhotic patients (notably including both treated and untreated patients; **Error! Reference source not found.**) (20). Further, in this study, where 407 (36.6%) patients had significant or severe fibrosis (i.e., METAVIR score ≥F2) at baseline, among new cirrhotic patients after a median follow-up of 3.0 years, 166 out of 174 (95.4%) patients had been classified as having METAVIR score ≥F2 at referral (20). These data support a fast rate of progression in patients with late-stage fibrosis. **Figure 2: Cumulative incidence of compensated cirrhosis in Romeo *et al.,* (2009) and Roulot *et al*., (2002) studies**	

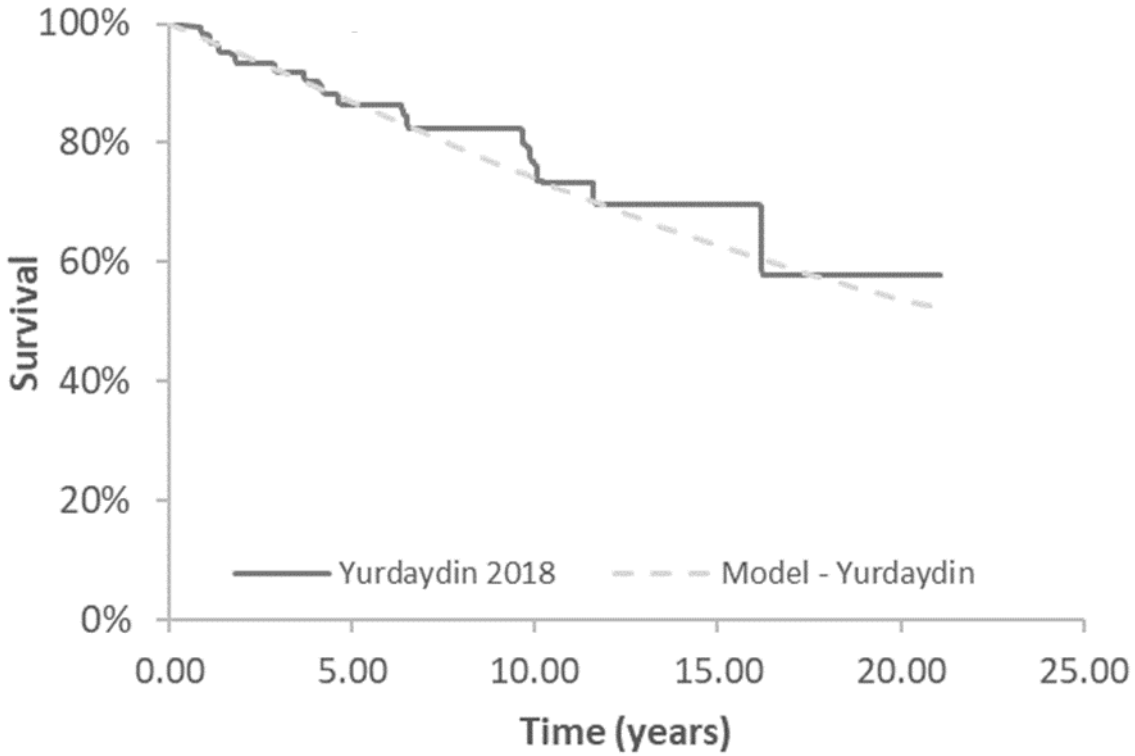
Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			 As shown in **Error! Reference source not found.** below, the model predictions for the incidence of compensated cirrhosis amongst the patients who are F0-F3 at model start is generally in alignment with findings from the Romeo *et al*., (2009) study. The incidence is slightly higher overall which may be supported given the results observed in Roulot *et al*., (2020) (20). **Figure 3: Cumulative incidence of compensated cirrhosis in Romeo 2009 and model Romeo predicted 2002 studies**	

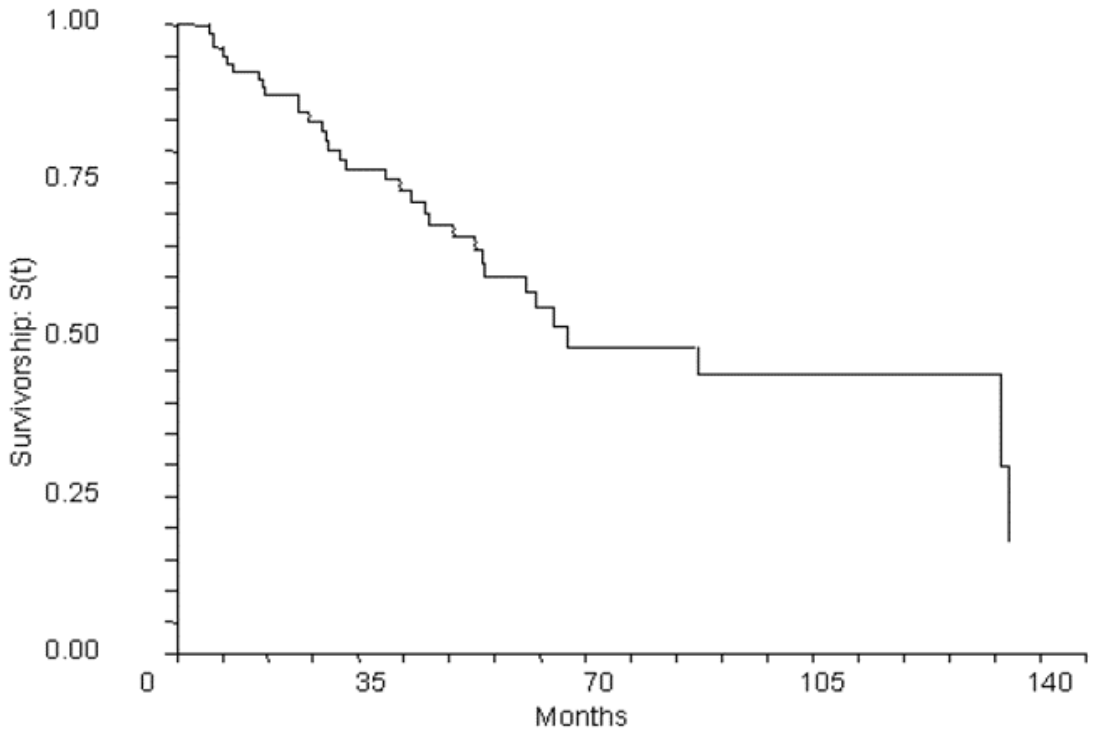
Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			 ***6.2.2 Decompensated cirrhosis*** In the Kamal *et* al., (2020) study, 337 patients with anti-HDV positivity, including 233 patients with HDV RNA viremia were retrospectively studied with a mean follow-up time of 6.5 years (range 0.5-33.1). In patients with HDV RNA positivity, 29.6% of patients had liver cirrhosis at baseline. 39.1% of patients with HDV RNA positivity and cirrhosis at baseline experienced hepatic decompensation and 3% of patients with HDV RNA positivity and without cirrhosis at baseline experienced hepatic decompensation (21). Cumulative decompensation-free survival is shown below in **Error! Reference source not found.**. Predictions from the model are similar to those from the Kamal *et* al., (2020) study (**Error! Reference source not found.**) (21). Further, the rate of hepatic decompensation in patients with cirrhosis at baseline was 10.2% per person-year, similar to the rate estimated for use in the economic model (10.67%). **Figure 4: Kaplan-Meier decompensation-free survival curves based on HDV RNA status from Kamal *et al*., (2020)**	

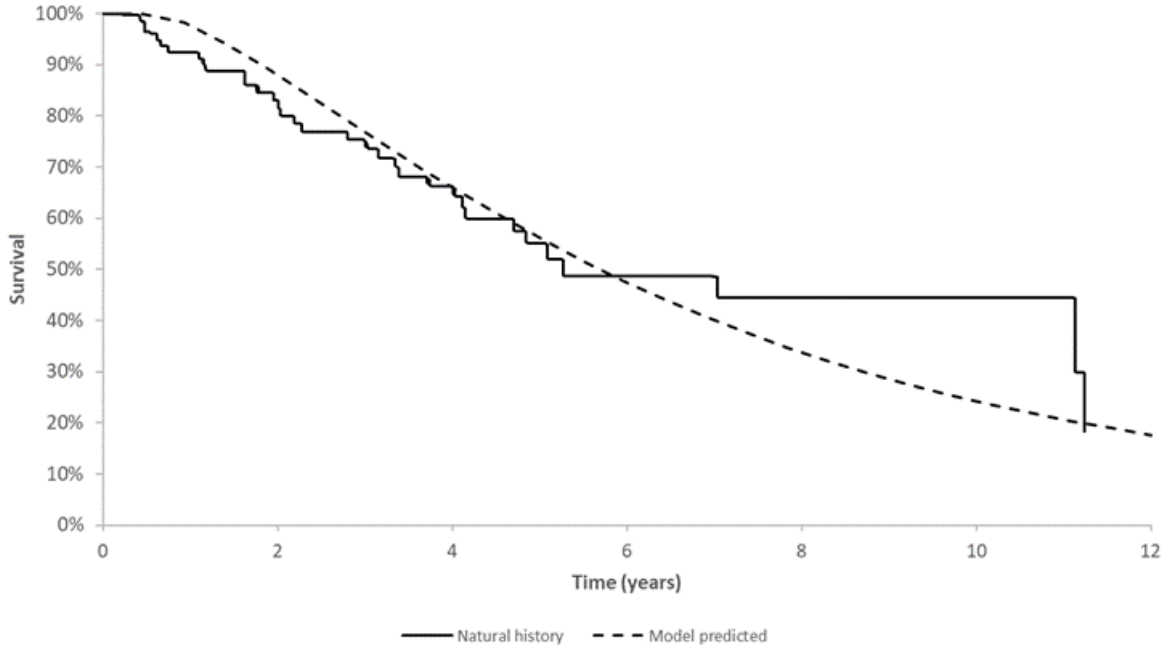
Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			 **Figure 5: Comparison of decompensation-free survival of patients from Kamal *et al*., (2020) vs. predictions from economic model**	

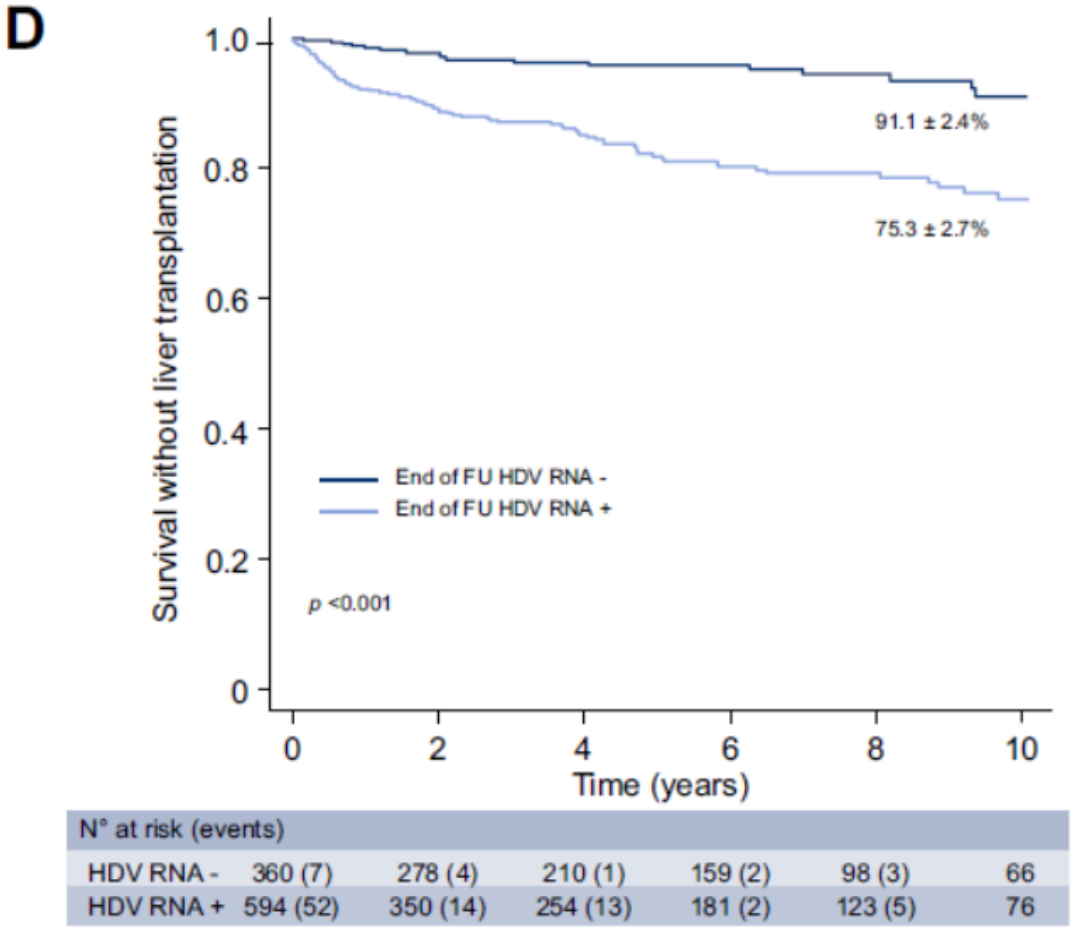
Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			 ***6.2.3 Hepatocellular carcinoma (HCC)*** In the Yurdaydin *et al.,* (2018) study, a hepatitis delta database was analysed for the effects of treatment duration on virologic response and clinical outcomes. 99 chronic hepatitis delta patients who received at least 6 months of interferon treatment were selected. Post-treatment median follow-up was 55 months (24-225 months). Of these patients, 35 achieved a maintained virologic response (MVR). In the non-responder patients, 22% (14/64) had cirrhosis present at baseline. HCC-free survival outcomes for patients without MVR, assumed to be most appropriate for comparison with BSC, are shown in Figure 6. Given the lack of data regarding the distribution of patients from F0-F3, a similar distribution of non-cirrhotic patients was assumed based on data from Romeo *et al*., (2009) (19). The model showed generally similar results for the cumulative incidence of hepatocellular carcinoma for BSC compared to those without MVR from the Yurdaydin *et* al., (2018) study (**Error! Reference source not found.**) (22).	

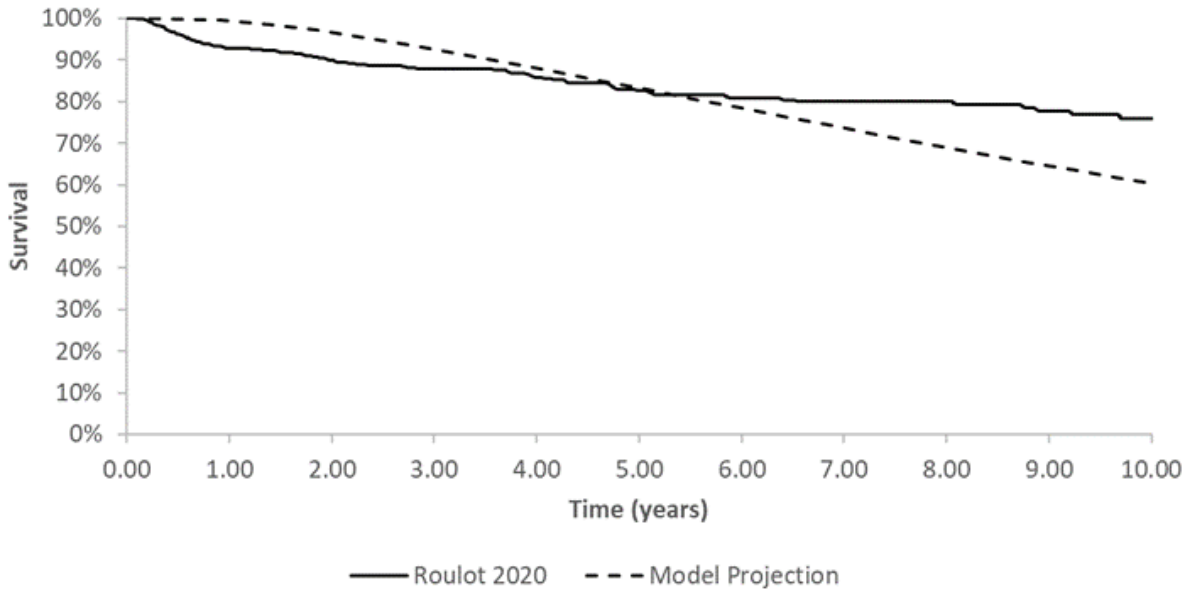
Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Figure 6: Kaplan-Meier hepatocellular carcinoma-free survival curve from Yurdaydin *et al.*, (2018) in patients with and without MVR  **Figure 7: Comparison of survival of patients from Yurdaydin *et al.*, (2018) vs. predictions from economic model**	

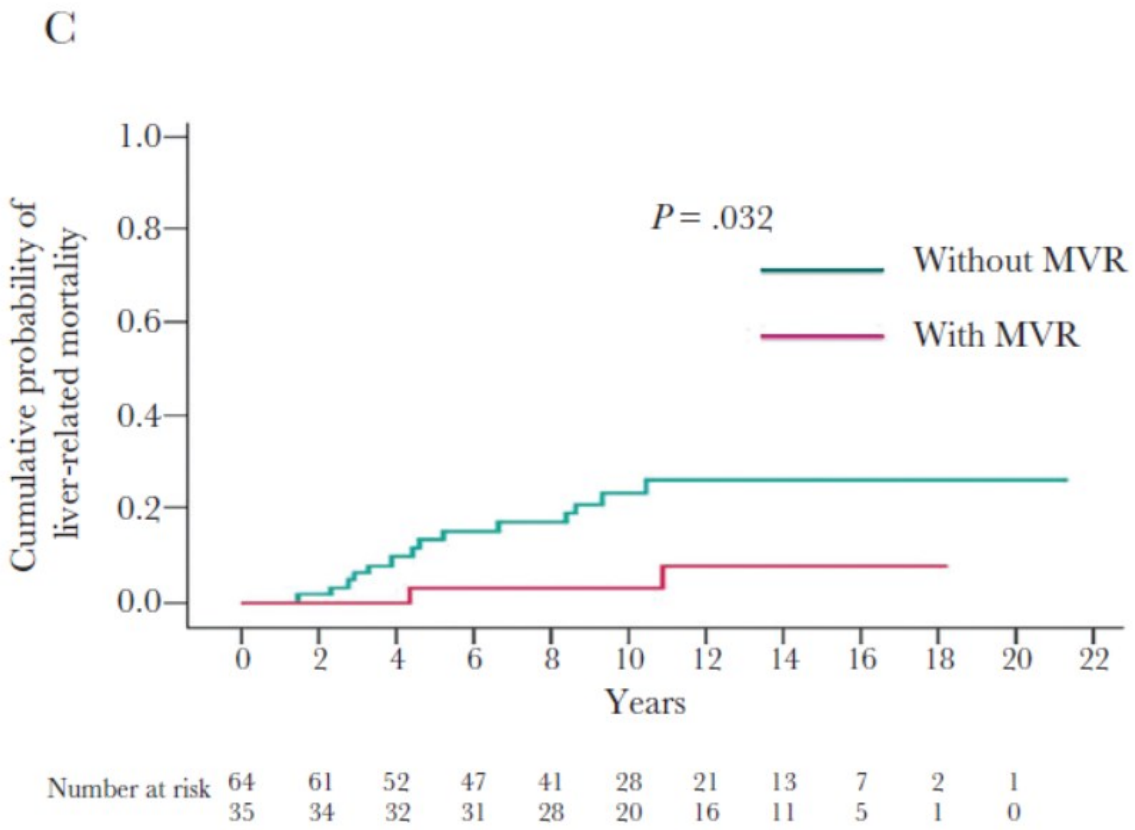
Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			 ***6.2.4 Liver-related mortality*** Three natural history studies were evaluated to compare the projections from the economic model regarding mortality. **6.2.4.1 Survival of compensated cirrho*sis (F4) patients*** The first study included 166 patients with compensated HDV-related cirrhosis diagnosed since 1994 and followed until death or 31st December 2004. Patients had a mean age of 40.7±7.9 years. The median survival was 58.3 months since the diagnosis of compensated cirrhosis, with a probability of survival after the diagnosis of compensated cirrhosis of 94.3%, 82.5%, and 51.5% at 1, 2, and 5 years, respectively (**Error! Reference source not found.**) (23). Predictions from a purely compensated cirrhotic (i.e., 100% F4) population in the model demonstrated strong alignment with those projected from this study (Figure 9).	

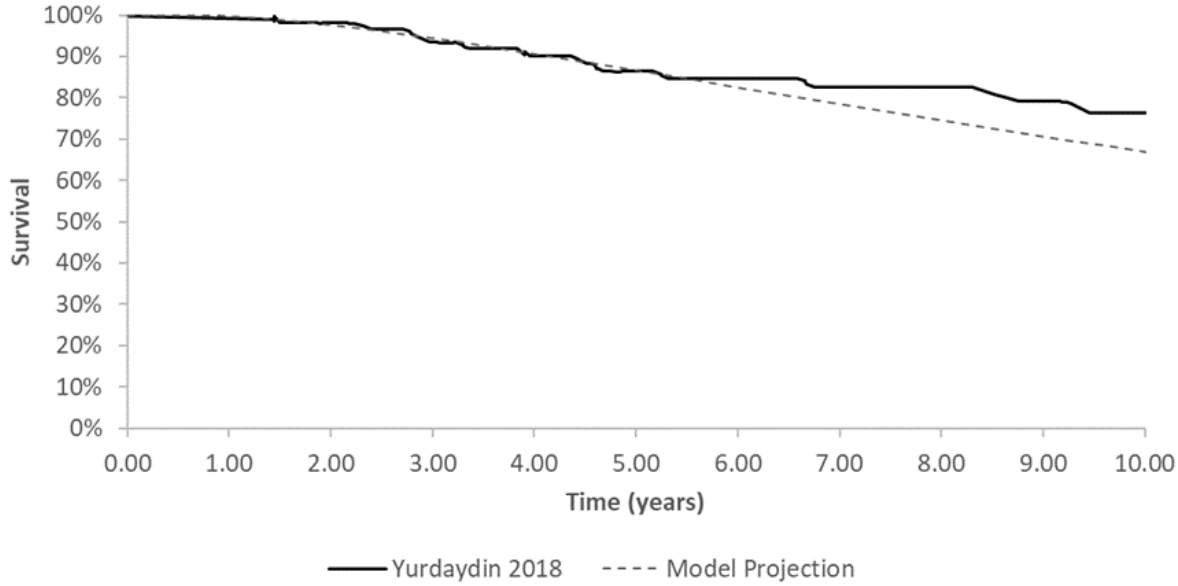
Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Figure 8: Kaplan-Meier survival curve of patients with compensated HBV-HDV cirrhosis from Gheorge *et al*., (2005)  ***6.2.4.2*** **Survival in broad F0-F4 population** To determine whether projections from the combined non-cirrhotic and cirrhotic populations aligned with natural history studies regarding mortality, two studies were selected based on availability of data for patients without HDV RNA - (Roulot *et* al., 2020) and for those without MVR due to treatment (Yurdaydin *et al*., 2018) (20, 22). **Figure 9: Comparison of survival of compensated cirrhosis patients from Gheorge *et al*., (2005) vs. predictions from economic model**	

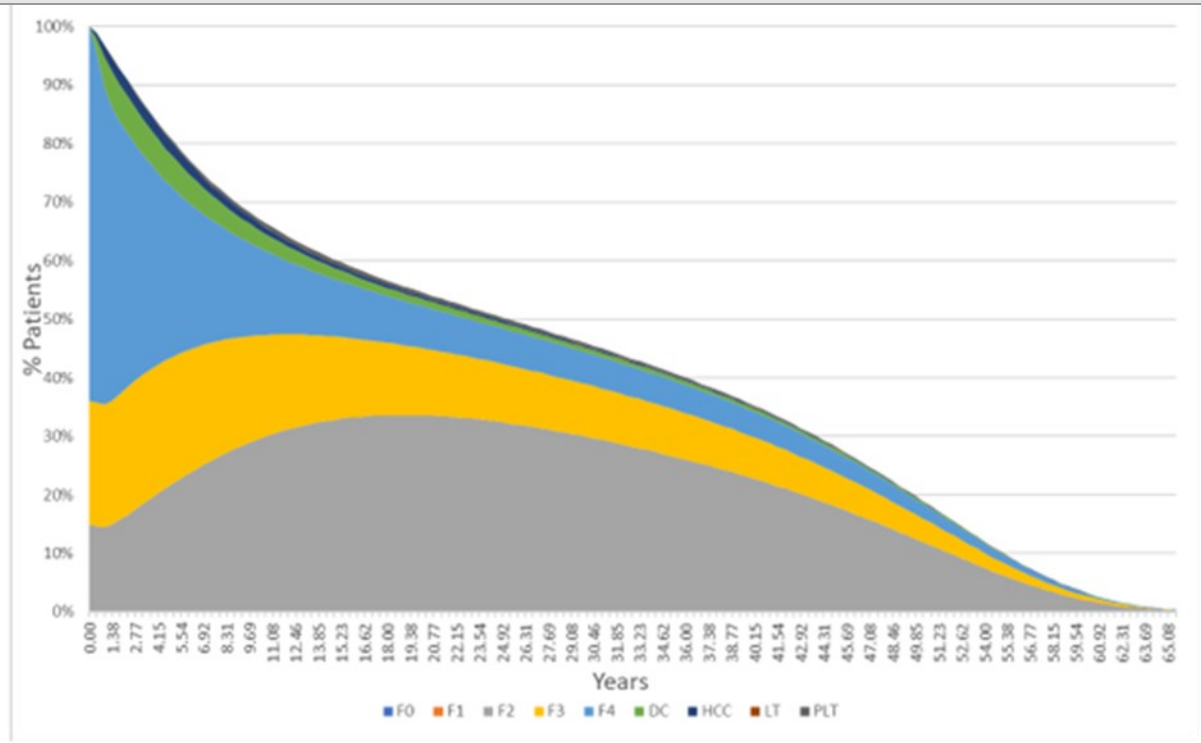
Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			 In the Roulot *et* al., (2020) study, at referral, 28.1% of patients had cirrhosis, 36.6% had significant or severe fibrosis (≥F2), and 16.8% had no or minimal fibrosis (F0-F1). The 5-year risk of death in the entire population, including patients who may have received treatment, was 20.2%. Survival according to HDV RNA status at the end of follow-up showed that patients with positive HDV viral load had a higher chance of death (hazard ratio 3.30, p<0.001; **Error! Reference source not found.**). Projections from the model are generally similar to those from the Roulot *et* al, (2020) study, though a low number of events towards the end of follow-up creates uncertainty about survival outcomes beyond 8 years (**Error! Reference source not found.**). **Figure 10: Survival without liver transplantation according to persistent HDV viremia before endpoint from Roulot *et al*., (2020)**	

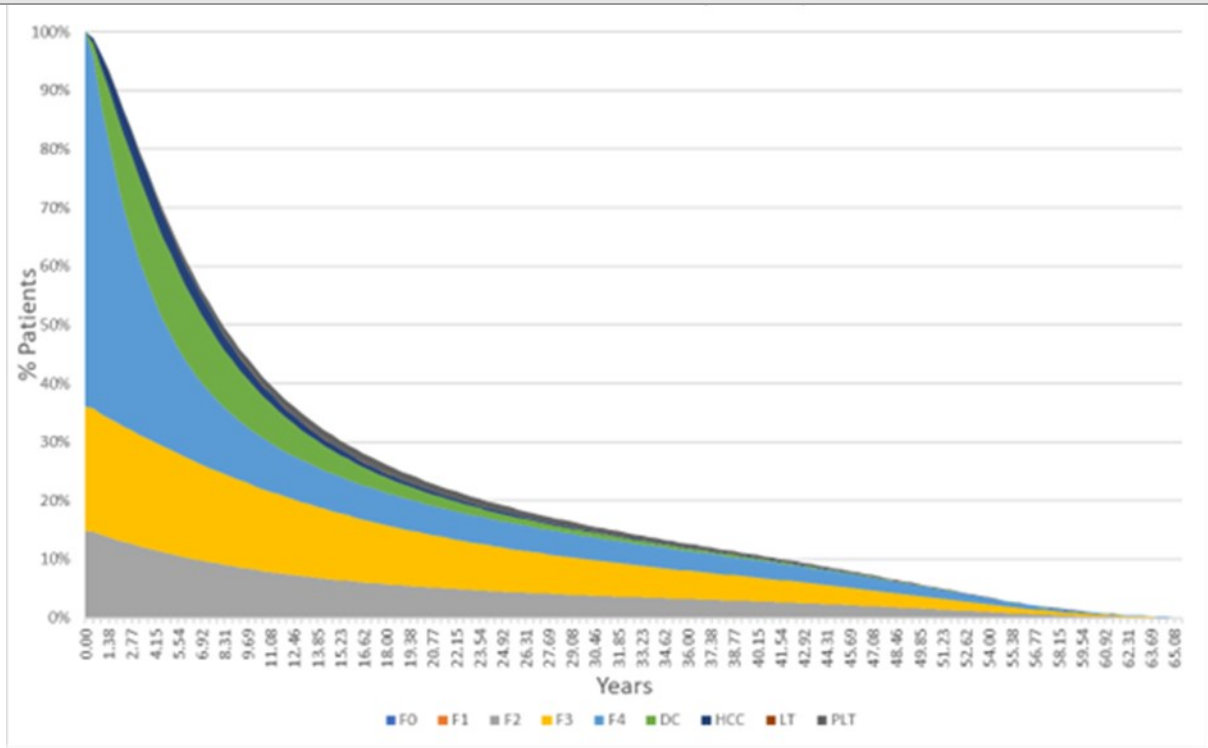
Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			 N° at risk (events) HDV RNA - 360 (7) 278 (4) 210 (1) 159 (2) 98 (3) 66 HDV RNA + 594 (52) 350 (14) 254 (13) 181 (2) 123 (5) 76 **Figure 11: Comparison of survival of F0-F4 HDV RNA+ patients from Roulot *et al*., (2020) vs. predictions from economic model**	

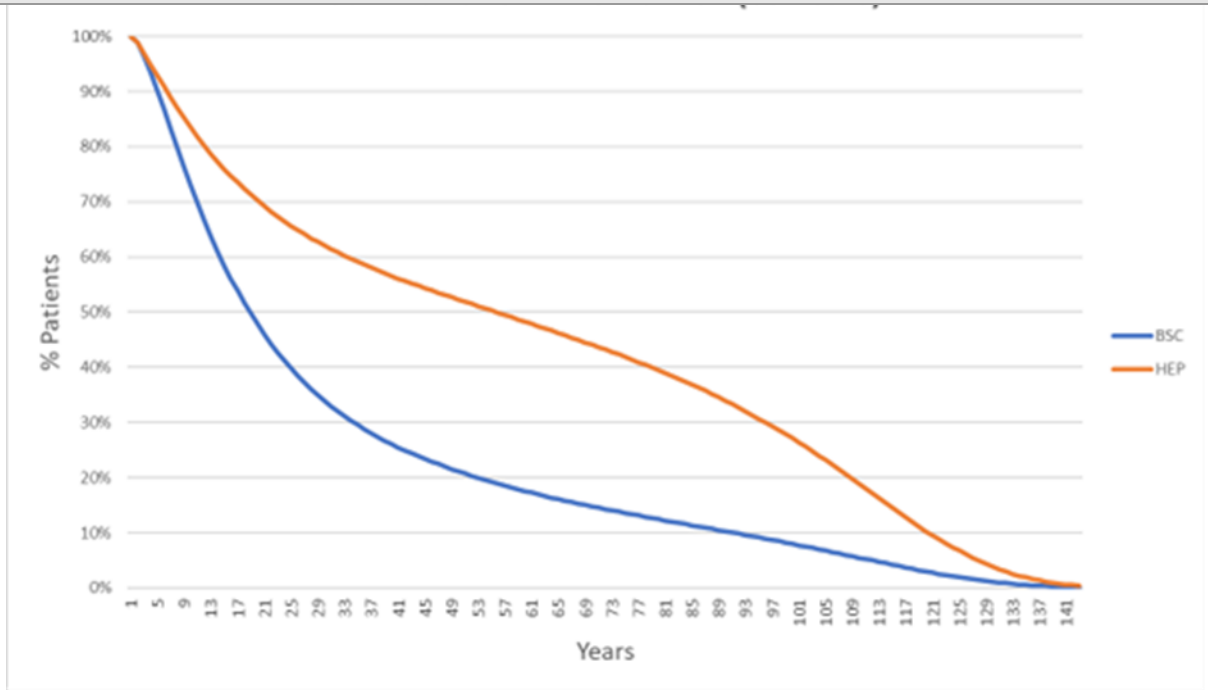
Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			 Survival outcomes in the Yurdaydin *et al*., (2018) study, for patients without MVR, assumed to be the most appropriate for comparison with BSC, are shown in **Error! Reference source not found.**. Given the lack of data regarding the distribution of patients from F0-F3, a similar distribution of non-cirrhotic patients was assumed based on Romeo *et al*., (2009). Given the relatively low number of observations (**Error! Reference source not found.**) after 10 years, these first ten years were analysed to compare model survival outcomes vs. the study. The model showed generally similar results for liver-related mortality for BSC compared to those without MVR from the Yurdaydin *et al*., (2018) study (**Error! Reference source not found.**). **Figure 12: Liver-related mortality stratified by MVR status in Yurdaydin *et* al., (2018)**	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			 **Figure 13: Comparison of survival of F0-F4 patients without MVR vs. predictions from economic model**	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			 **6.3 Health state occupancy** The committee requested graphical representations of fibrosis health state occupation over time from the economic model. We have created these graphs for both arms, in addition to a graph which shows the survival over the time horizon. Results are reported in Figure 1 to Figure 3. These can also be found in the RESULTS sheet of the executable model. **Figure 14: Health state occupancy, Bulevirtide arm**	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			 **Figure 15: Health state occupancy, BSC arm**	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			 **Figure 16: Overall survival**	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
				
	Consultee	NHS England	We have reviewed the draft guidance and committee papers. We agree the scope of the review included the relevant evidence.	Comment noted. Thank you.
	Consultee	NHS England	The summaries provided reasonable reviews of the current evidence on the use of bulevirtide for the treatment of hepatitis delta infection.	Comment noted. Thank you.
	Consultee	NHS England	We agree there is a need for some further clarification in the submitted application, particularly in relation to (a) selection of patients using non-invasive fibrosis tests, (b) positioning as a primary therapy or purely for those intolerant / unresponsive to interferon and (c) duration of therapy and stopping rules.	Comment noted. Thank you. The committee further discussed these issues at the second committee meeting.

Document processed	Organisation name – Stakeholder or respondent	Disclosure on tobacco funding / links	Number of comments extracted	Comments

Bulevirtide for treating chronic hepatitis D [ID3732]

Company response to NICE appraisal consultation document

November 2022
Version 2

Contents

Abbreviations

AASLD	American Association for the Study of Liver Diseases
ACD	Appraisal committee document
ALT	Alanine aminotransferase
AUROC	Area under the receiver operating characteristic
BSC	Best supportive care
CC	Compensated cirrhosis
CG	Clinical guideline
CHB	Chronic hepatitis B
CHD	Chronic hepatitis D
CLAD	Censored least absolute deviations
DCC	Decompensated cirrhosis
EAG	Evidence assessment group
EASL	European Association for the Study of the Liver
EQ-5D	EuroQol 5 Dimensions
HCC	Hepatocellular carcinoma
HDV	Hepatitis delta virus
ICER	Incremental cost-effectiveness ratio
IFN	Interferon
kPa	Kilopascal
LYG	Life years gained
MVR	Maintained virologic response
NHSE&I	NHS England & NHS Improvement
NICE	National Institute for Health and Care Excellence
OLS	Ordinary least squares
PEG-IFN	Peginterferon alpha-2a
QALY	Quality-adjusted life year
RNA	Ribonucleic acid
SVR	Sustained virologic response
TA	Technology appraisal
TDF	Tenofovir disoproxil fumarate
UKHSA	UK Health Security Agency

List of tables

List of figures

Executive summary

The Company is grateful for the opportunity to respond to the appraisal consultation document (ACD). While we are disappointed that bulevirtide did not receive an initial positive recommendation for treating chronic hepatitis D (CHD) with compensated liver disease in adults[1], we are pleased that the appraisal committee recognizes that there is a significant unmet need for effective treatments in this population because the current treatment options are limited.

In the ACD, the Committee noted that the clinical evidence collected from the pivotal MYR 301 clinical study showed bulevirtide is effective compared with current standard of care and acknowledged the large benefit for patients who had treatment with bulevirtide at Week 48. However, the Committee also considered that there are uncertainties surrounding the duration of on-treatment effect for bulevirtide, as well as uncertainties relating to how eligible patients would be identified using METAVIR staging. The Committee noted that this translated into uncertainty around the estimates of cost-effectiveness.

In Section 3.16 of the ACD (pages 14-16), the Committee sets out its preferred assumptions and notes specific areas of uncertainty. The Company has addressed these topics in our response to the ACD in the analyses and discussion that follows. The Committee also requested a range of scenario analyses along with additional data. Where feasible, the Company has addressed each of the areas of uncertainty and has carried out additional scenario analyses, the results of which are reported within the associated topics of this response.

A patient access scheme (PAS) has been approved by PASLU for NHSE&I. The PAS involves a simple discount from list price. In response to the ACD, the confidential net price has been decreased from £[redacted] to £[redacted] per pack.

[1] Bulevirtide is indicated for the treatment of chronic HDV infection in plasma (or serum) HDV-RNA positive adult patients with compensated liver disease

Summary conclusions are as follows:

1. **The company's proposed positioning in people with METAVIR stage ≥F2 (Topic 1)**
   - The Company's proposed positioning for bulevirtide aligns with existing National Institute for Health and Care Excellence (NICE) clinical guideline (CG) 165.
   - Subgroup analysis of patients in MYR 301 in METAVIR fibrosis stages ≥F2 according to equivalent FibroScan cut-offs were conducted; the majority of MYR 301 patients ([redacted]%)[2] had a liver stiffness measurement consistent with METAVIR ≥F2 at baseline. The subgroup analysis and overall population (full analysis set) is therefore relevant to the decision problem. Response rates in the subgroup analysis are consistent with response rates in the overall population (presented in the Company's original submission) further demonstrating the efficacy of bulevirtide in patients with a high unmet need.
   - Cost-effectiveness analysis using response data from the subgroups defined by liver stiffness demonstrate the incremental cost-effectiveness ratio (ICER) to be robust and the ICER for bulevirtide ranging from £22,228 to £24,298 per quality-adjusted life year (QALY) gained when considering the 1.2 severity modifier.

2. **The mean age of people diagnosed with hepatitis D in the UK (Topic 2)**
   - The mean age of people diagnosed with hepatitis D in the UK determined by the UK Health Security Agency (UKHSA) does not alter eligibility for a severity weight when applied to the company base-case. The mean age of people with hepatitis delta virus (HDV) is estimated to be 36.9 years, however the data is skewed meaning that the median age (35.0 years) is a more appropriate measure of average age and is consistent with the average age used in the Company's base case analysis (35.1 years, as per Spaan *et al.,* 2020) (1).
   - UKHSA data demonstrates that the majority of patients (55%) with hepatitis D are young, being 36 years of age or less[3] (2).

[2] Based on a transient elastography of ≥8.0 kPA.
[3] The 1.2x QALY modifier threshold in the EAG's model is [redacted] years.

- Cost-effectiveness analysis using the UKHSA data further demonstrates that there is a significant QALY shortfall amongst people living with CHD compared to the expected future health without the condition over the remaining lifetime of the patient; meaning bulevirtide qualifies for the 1.2 severity modifier.
- Bulevirtide is a cost-effective treatment option compared to best supportive care (BSC); the ICER ranging from £24,061 to £24,433 per QALY gained when considering the 1.2 severity modifier and the UKHSA median vs. mean age.

3. Progression/regression rates of combined responders (Topic 3)

- A low but not zero risk of progression through fibrosis stages for combined responders was explored in the model, resulting in a negligible impact on the Company's base-case ICER (with severity modifier of 1.2) (+£463).
- A low but not zero risk of progression to hepatocellular carcinoma (HCC) for combined responders was explored in the model, resulting in a negligible impact on the Company's base-case ICER (with severity modifier of 1.2) (+£458).
- A lower probability of fibrosis regression for combined responders in the model had a relatively modest impact on the Company's base-case ICER (with severity modifier of 1.2) (+£807). Regression rates in the model were informed by observed responses to antiviral treatments in chronic hepatitis B (CHB) and chronic hepatitis delta (CHD) patients in the real-world. Given that these rates of regression were informed by real-world evidence in patients with viral hepatitis, we do not consider scenario analyses for lower regression rates requested by committee to be realistic.
- The Company's base-case ICERs range from £24,519 to £24,868 per QALY gained across these scenario analyses (including the 1.2 severity modifier).

4. Treatment duration beyond 48 weeks in MYR 301 (Topic 4)

- The Company's revised base case now includes the EAG's preferred assumption of continuing treatment in patients who develop HCC. The impact of the ICER is negligible, increasing by £6 from £24,055 to £24,061 per QALY gained (including the 1.2 severity modifier).
- While assuming the same continuation rules for virologic and combined responders increases the ICER, we note that clinicians were unsure that

virologic responders would have the same continuation rules and that this may only apply to specific cases. The associated ICERs (including the 1.2 severity modifier) were £28,957 to £29,332.

- As requested by the Committee, the impact of stopping treatment in patients with virus eradication was explored. Note, the Company's revised base-case include this assumption. Continuing treatment in patients with evidence of virus eradication increases the ICER (including the 1.2 severity modifier) from £24,061 (company base-case) to £27,165 per QALY gained.

5. **The size of utility gain for combined responders (Topic 5)**
    - NICE methods guidance stipulates that where possible utilities from the technology's clinical trials should be used in the economic model. The Company's choice of regression model for generating utilities was underpinned by observed ceiling effects from the MYR 301 data.
    - Utility gains for patients with sustained virologic response (SVR) in other hepatitis technology appraisals has been slightly lower (different by ≤0.02) than that observed for combined responders in MYR 301, however this may be explained by differences in the type of hepatitis infection and population.
    - The impact on the ICER of varying the size of the utility gain for combined responders was explored by assuming 75% and 50% of the current MYR 301 responder utility gain; the associated ICER were £24,605 and £25,175 respectively (including the 1.2 severity modifier).

6. **The long-term survival for people on standard care, in the absence of bulevirtide (Topic 6)**
    - The Company has validated the progression and survival rates predicted by the economic model with those in the published CHD literature by comparing Kaplan-Meier plots with survival plots extracted from the model.
    - There was close alignment between the model predictions and the published literature, with divergence only observed at later timepoints where costs and outcomes are discounted.
    - The analysis demonstrates that that Company's base-case assumptions associated with the natural history of CHD are appropriate.

The NICE health technology evaluation manual (2022) notes that a higher degree of uncertainty regarding estimates of cost-effectiveness is acceptable for health technologies for which evidence generation is particularly difficult, specifically for rare diseases and innovative technologies (see section 6.2.34, pp. 157).

The majority of the scenarios requested by the Committee have a relatively modest impact on the ICER. In the majority of cases the ICER associated with bulevirtide remains with the £20,000 to £30,000 per QALY gained range normally considered a cost-effective use of NHS resources. This is particularly compelling given that CHD is a rare disease and bulevirtide is an innovative first-in-class treatment with GB orphan drug designation.

The Company accepts a number of the External Assessment Group (EAG) preferred assumptions (the majority of which were not discussed in part 1 of the appraisal committee meeting) and is willing to adjust its preferred base case accordingly.

The Company has therefore updated its current base case assumptions with the following changes:

i. Average age of people diagnosed with hepatitis D in the UK based on UKHSA median age of 35.0 years, further supported by Spaan *et al.* (2020).
ii. Treatment stopped for those with convincing evidence of virus eradication (see section 3.11 of the ACD). Clinical experts confirmed that patients with convincing evidence of virus eradication, treatment would likely be stopped. This scenario had previously been conservatively excluded from the Company base-case, but as the Company is aware that this is a feasible scenario in UK clinical practice, this has now been included in the post-committee base-case.
iii. MYR 301 data not extrapolated beyond Week 48; note this is a conservative assumption considering the observed trend of increasing response rates across the first 48 weeks of treatment with bulevirtide.
iv. Age-related utility decrements included.
v. Health state utilities based on MYR 301.
vi. Post-liver transplant utility value set to MYR 301.
vii. Assuming that patients who develop HCC remain on bulevirtide.

The revised Company base case cost effectiveness results are presented in Table 1. It can be seen that the severity-weighted ICER lies below the willingness-to-pay threshold of £30,000 per QALY gained using a severity modifier of 1.2x, demonstrating that bulevirtide not only provides significant benefits in terms of improved patient prognosis, but is a cost-effective treatment for the NHS.

Table 1: Company's ACD revised base case cost-effectiveness estimates

Interventions	Total costs (£)	Total QALYs	Incremental costs	Incremental QALYs	Incremental QALYs – 1.2 severity weighting	ICER	ICER - 1.2 severity weighting
BSC[4]	[redacted]	[redacted]	-	-	-	-	-
Bulevirtide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,874	£24,061

The ICER does not reflect additional benefits associated with bulevirtide

The Committee noted in the ACD that there are several benefits of bulevirtide that were not captured by the QALY calculation.

Hepatitis D is a rare disease and bulevirtide is the first licensed treatment option for the treatment of CHD. The Committee were of the opinion that bulevirtide is an innovative treatment option which is well tolerated, and which addresses this unmet need. Bulevirtide is a first-in-class medicine with GB orphan designation (PLGB 50662/0002/OD1) and promising innovative medicines (PIM) designation. The Committee heard from clinical experts that bulevirtide represents a step change in the management of the CHD.

The Committee acknowledged that bulevirtide reduces the viral load in infected people thereby preventing the spread of infection; a significant benefit not captured by the QALY calculation. Additionally, the Committee heard from a patient advocacy group representative and clinicians concerning the stigma associated with blood-borne viruses. Clinical advisers have advised the Company that the introduction of a licenced treatment option such as bulevirtide is expected to bring about healthcare system-wide benefits as clinicians and patients will now have an effective treatment option such as encouraging HDV testing and reducing regional variation in practice.

[4] Please note that BSC results remain unchanged.

Early diagnosis and treatment of HDV is expected to positively impact health outcomes and reduce costs associated with healthcare resource use. Reducing and/or delaying the progression to more severe disease including decompensated cirrhosis (DCC), liver cancer, and liver transplant, is expected to result in a significant reduction to healthcare costs and a substantial QALY gain. In the appraisal committee meeting, the Committee acknowledged that HDV disproportionately affects some groups of people such as Black African people and economic migrants.

The Company recognises that the pivotal registrational phase III study of bulevirtide, MYR 301, is ongoing. However, the Company is of the strong opinion that based on the totality of evidence, the uncertainty associated with an innovative treatment for a rare disease is proportionate; bulevirtide represents a cost-effective treatment option and should therefore be recommended.

Topic 1 The Company's proposed positioning in people with METAVIR stage ≥F2

ACD section 3.3 *"The company presented data from the full analysis set from MYR 301, which included people with all METAVIR fibrosis stages (F0 to F4), so it was unclear why the company positioned bulevirtide only for METAVIR stage F2 and above…"*

ACD section 3.4 *"METAVIR staging is done using a liver biopsy, which is invasive and carries a morbidity and mortality risk. Therefore, many people refuse this procedure…* i*t would be useful for the company to present data using transient elastography rather than liver biopsy (METAVIR staging) to assess fibrosis"*

Company response:

- Existing NICE guidelines CG165 advise that peginterferon alfa-2a (PEG-IFN) should only be initiated in patients co-infected with hepatitis D "*who have evidence of significant fibrosis (METAVIR stage greater than or equal to F2 or Ishak stage greater than or equal to 3)*". The Company's proposed positioning for bulevirtide aligns with this.
- Transient elastography (FibroScan) scores were collected for all patients in the MYR 301 study. We were able to identify subgroups of patients in MYR 301 in fibrosis stages greater than or equal to F2 (≥F2) according to published FibroScan cut-offs (≥7.25 kPa or ≥8.0 kPa) and found that [redacted]% of MYR 301 patients were ≥F2.
- Scenario analyses demonstrate the ICER to be robust in the subgroup of patients with FibroScan scores considered to align with fibrosis stage ≥F2 in UK clinical practice.

1.1 Summary

The committee queried the Company's proposed positioning of bulevirtide for the treatment of CHD in adult patients with compensated liver disease and evidence of significant fibrosis (METAVIR stage ≥F2), given the METAVIR F-stage distribution of patients recruited to MYR 301. They further queried how patients with METAVIR stage ≥F2 would be identified in clinical practice. In section 1.2, we explain that the

identification of patients with significant fibrosis is already required to identify patients eligible for treatment with peginterferon alpha-2a (PEG-IFN) in the UK and that this is based on transient elastography (FibroScan) score cut-off points.

Liver stiffness, as measured by transient elastography (FibroScan) was collected for all patients enrolled onto the pivotal MYR 301 clinical study. As a result, it was possible to assign patients in MYR 301 to METAVIR fibrosis stages based on their FibroScan score in a manner aligned with UK clinical practice, and identify subgroups for patients with METAVIR stage ≥F2 according to their FibroScan score. When using this approach, we found that an overwhelming majority (≥[redacted]%) of MYR 301 patients at baseline in the bulevirtide 2 mg and delayed treatment arms would be deemed to be ≥F2 according to UK clinical practice. In summary, we have demonstrated that the proposed positioning of bulevirtide is in line with the existing NICE guideline CG165, that identification of patients in METAVIR fibrosis stage ≥F2 is feasible in clinical practice and that the MYR 301 data are generalisable to that population.

Furthermore, in section 1.3 we undertake a scenario analysis in the model where we incorporate the responder data for MYR 301 patients identified as being ≥F2 according to both FibroScan and METAVIR score. The Company's ICERs remain largely unchanged in these scenarios, varying only slightly compared with the base case.

1.2 Identification of patients in METAVIR fibrosis stage ≥F2 in clinical practice

The treatment options for patients with chronic hepatitis delta (CHD) are limited. NICE guideline CG165 recommends that adults with chronic hepatitis B (CHB) and hepatitis delta infection, who have evidence of significant fibrosis (METAVIR stage ≥F2 or Ishak stage ≥3), should be offered a 48-week course of off-label PEG-IFN (3). Similarly, bulevirtide is proposed to treat adults with CHD with METAVIR stage ≥F2, albeit patients are required to have compensated liver disease and should not have responded well enough to a prior course of interferon-based therapy (hereafter referred to as IFN-based therapy), should have an intolerance to IFN-based therapy, or should have a contraindication to IFN-based therapy.

To determine METAVIR stage, and thus level of liver fibrosis, patients are required to undergo a liver biopsy. However, as discussed in the draft guidance consultation, clinical experts highlighted that liver biopsy is an invasive procedure which carries a morbidity and mortality risk to the patient. As such, many patients refuse to undergo

this procedure. Clinical experts explained that in clinical practice, transient elastography (FibroScan), a non-invasive test recommended in NICE guideline CG165 to assess liver disease in all adults diagnosed with chronic hepatitis B (CHB), is widely used to assess eligibility for PEG-IFN in CHD patients. Experts highlighted that they would like to use transient elastography to determine the patient eligibility for treatment with bulevirtide, as opposed to undertaking liver biopsy.

FibroScan can identify significant fibrosis in patients with viral hepatitis and advanced liver disease to a good degree of accuracy (4, 5). A FibroScan threshold that corresponds to significant fibrosis (METAVIR stage ≥F2) in CHD has not yet been published, perhaps due to the orphan nature of the disease, and consultation with clinical experts confirms that heterogeneity exists regarding the appropriate cut-off value. In the absence of a clinical expert consensus, we conducted a literature search to identify potential cut-offs that could be applied to the Company's FibroScan data. Based on this literature search, we identified two thresholds. A meta-analysis by Qi *et al*., (2018) assessing the diagnostic accuracy of transient elastography in 7,808 CHB patients identified an optimal threshold value of ≥7.25 kPa at baseline to determine the presence of significant fibrosis (6). In addition, 2021 European Association for the Study of the Liver (EASL) clinical practice guidelines on non-invasive tests for evaluation of liver disease and severity and prognosis strongly recommend a FibroScan score of ≥8.0 kPa to confirm METAVIR fibrosis score ≥F2 (4).

FibroScan scores were collected in the pivotal MYR 301 study in all patients at baseline and Week 48. We have utilised both literature cut-offs to define subgroups of patients with a METAVIR fibrosis score of ≥F2 given their FibroScan score. [redacted]% and [redacted]% of patients in the bulevirtide 2 mg and delayed treatment arms in MYR 301 had a FibroScan score of ≥7.25 kPa and ≥8.0 kPa, respectively, indicating that an overwhelming majority of patients in MYR 301 study were in line with the proposed positioning in patients with a METAVIR fibrosis score of ≥F2.

Furthermore, we carried out a scenario analysis in the model using the response rates (both combined and virologic) of these subgroups of patients in fibrosis stage ≥F2. The response rates of the subgroups, compared with the overall population, are shown in Table 2. Results of the scenario analyses in the subgroups of patients with a transient elastography score aligned with METAVIR stage ≥F2 in UK clinical practice can be

found below. We also present, alongside this, the results of the subgroup analysis based on the METAVIR score collected in MYR 301 (noting that biopsy data were unavailable for [redacted] of patients at baseline across the delayed treatment and bulevirtide 2 mg arms). The METAVIR scores may not be missing at random, given that more advanced patients may have been more likely to have had a liver biopsy in the past and may therefore have been less willing to have one as part of MYR 301. The results of both scenario analyses show the ICER to be robust in the subgroup of patients estimated to be in ≥F2 according to their FibroScan score.

1.3 Scenario using transient elastography (FibroScan)

Transient elastography is the most widely available and validated non-invasive test to assess the level of fibrosis in patients with advanced liver disease and is recommended by both the American Association for the Study of Liver Diseases (AASLD) and EASL (4, 7). EASL clinical practice guidelines on non-invasive tests for the evaluation of liver disease severity and prognosis stipulate that the diagnostic accuracy of transient elastography for detecting significant fibrosis in patients with advanced liver disease is good, with diagnostic accuracy (area under the receiver operating characteristic curve [AUROC]) around 0.85 (4). Similar AUROCs were detected in meta-analyses describing the diagnostic accuracy of transient elastography for predicting liver fibrosis in patients with CHB. Meta-analyses of studies comprising CHB patients define an optimal cut-off value of transient elastography for diagnosing METAVIR stage ≥F2 as 7.2 kPa (5, 6). However, differences in the cut-off value for METAVIR stage ≥F2 were present in the studies analysed in the meta-analyses, supporting claims by clinical experts that there is some heterogeneity regarding the appropriate cut-off values.

As a result, we have explored three subgroup analyses based on combining response at Week 24 and 48 by METAVIR Score (≥F2) with two published corresponding baseline liver stiffness measures (FibroScan ≥8.0kPA and FibroScan ≥7.25 kPA) (4, 6). As no extrapolations could be carried out for the subgroups in time for this response, the extrapolations are derived using the odds ratios of response rates between the extrapolated and observed data in the overall population. The results of these analyses are presented in Table 4 to Table 6.

Table 2: Results of the subgroup analyses for virologic response

	Bulevirtide 2 mg (n=49)	Delayed treatment (n=51)
Overall population		
n	**49**	**51**
Proportion of responders at Week 24, n (%)	[redacted]	[redacted]
Proportion of responders at Week 48, n (%)	[redacted]	[redacted]
Difference at Week 48	[redacted]	
METAVIR stage ≥F2* subgroup		
n	[redacted]	[redacted]
Proportion of responders at Week 24, n (%)	[redacted]	[redacted]
Proportion of responders at Week 48, n (%)	[redacted]	[redacted]
Difference at Week 48	[redacted]	
FibroScan score ≥7.25 kPa subgroup (TE cut-off based on Qi *et al.,* 2018)		
n	[redacted]	[redacted]
Proportion of responders at Week 24, n (%)	[redacted]	[redacted]
Proportion of responders at Week 48, n (%)	[redacted]	[redacted]
Difference at Week 48	[redacted]	
FibroScan score ≥8.0 kPa subgroup (TE cut-off based on EASL, 2021)		
n	[redacted]	[redacted]
Proportion of responders at Week 24, n (%)	[redacted]	[redacted]
Proportion of responders at Week 48, n (%)	[redacted]	[redacted]
Difference at Week 48	[redacted]	

* Note that [redacted]% of patients had missing data for METAVIR fibrosis score at baseline, hence the much smaller sample size. TE = transient elastography (e.g., FibroScan).

Table 3: Results of the subgroup analyses for combined response

	Bulevirtide 2 mg (n=49)	Delayed treatment (n=51)
Overall population		
n	**49**	**51**
Proportion of responders at Week 24, n (%)	[redacted]	[redacted]
Proportion of responders at Week 48, n (%)	[redacted]	[redacted]
Difference at Week 48	[redacted]	
METAVIR stage ≥F2* subgroup		
n	[redacted]	[redacted]
Proportion of responders at Week 24, n (%)	[redacted]	[redacted]
Proportion of responders at Week 48, n (%)	[redacted]	[redacted]
Difference at Week 48	[redacted]	
FibroScan score ≥7.25 kPa subgroup		
n	[redacted]	[redacted]
Proportion of responders at Week 24, n (%)	[redacted]	[redacted]
Proportion of responders at Week 48, n (%)	[redacted]	[redacted]
Difference at Week 48	[redacted]	
FibroScan score ≥8.0 kPa subgroup		
n	[redacted]	[redacted]
Proportion of responders at Week 24, n (%)	[redacted]	[redacted]
Proportion of responders at Week 48, n (%)	[redacted]	[redacted]
Difference at Week 48	[redacted]	

* Note that [redacted]% of patients had missing data for METAVIR fibrosis score at baseline, hence the much smaller sample size.

Table 4: Scenario applying responses from METAVIR score ≥F2

Analysis	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	Base-case ICER (£/QALY)
Company	[redacted]	6.31	[redacted]	£26,673	£28,874
Company with severity modifier				£22,228	£24,061

Table 5: Scenario applying responses from FibroScan score ≥7.25 kPA

Analysis	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	Base-case ICER (£/QALY)
Company	[redacted]	4.79	[redacted]	£29,158	£28,874
Company with severity modifier				£24,298	£24,061

Table 6: Scenario responses from FibroScan score ≥8.0 kPA

Analysis	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	Base-case ICER (£/QALY)
Company	[redacted]	4.80	[redacted]	£29,114	£28,874
Company with severity modifier				£24,262	£24,061

Topic 2 The mean age and cirrhosis status of people diagnosed with hepatitis D in the UK

ACD section 3.7 *"People in Spaan et al. had a baseline age of 35 years and 60% had cirrhosis. In MYR 301 the baseline age was 42 years and 47% had cirrhosis... The company also presented data published by Public Health England (now the UK Health Security Agency [UKHSA]) on routine blood-borne virus testing. The median age between 2011 to 2020 was around 36 years*

ACD section 3.16 *"The committee noted that it would like to see the mean age and cirrhosis status of UK patients at diagnosis based on UKHSA data"*

Company response:

- The mean age of people diagnosed with hepatitis D in the UK determined by UKHSA does not alter the eligibility for a severity weight when applied to the company base-case.
- A significant proportion of patients with hepatitis D are young, and the inability to apply a severity modifier due to a fraction of patients being older is discriminatory towards this patient population with a large unmet need.

2.1 Summary

In the absence of UK clinical study sites in the pivotal MYR 301 clinical study, the Company felt it was most appropriate to use baseline characteristics from Spaan *et al.* (2020), a retrospective analysis of 107 patients with CHD in the UK (4), in the economic model. Data on the median age of patients with CHD, collected by UKHSA from 2011 to 2020, was also presented to the committee, however the committee considered that UKHSA data on mean (rather than median) age at baseline would be more helpful to increase certainty in the cost-effectiveness results and the severity weighting applied to bulevirtide, despite the age distribution being skewed to the left e.g., the majority of patients being young.

UKHSA confirmed that the median age was 35.0 years (n= [redacted] patients) for patients when HDV ribonucleic acid (RNA) was first detected with a mean age [redacted] years. When considering the cohort of patients who are currently alive, the median age remained at 35 years (n= [redacted] patients) with the mean age for patients when HDV

RNA was first detected decreased to [redacted] years (5). This data supports the Company's original base case analysis which assumed an average age of 35.1 years as per Spaan et al. (2020) (4). The data on mean age of patients with CHD at baseline in the UK supplied by UKHSA has a minor impact on the ICER (see Table 7 below) and does not alter the eligibility for a severity weighting of 1.2 when applied to the Company base-case.

UKHSA data on baseline age at diagnosis implies that the majority of CHD patients in the UK are young, approx. 55% being age [redacted] years or younger which corresponds to the threshold for the severity modifier in the EAG's model. The Company is therefore of the opinion that the severity modifier should be applied. The Committee noted in the draft guidance the high disease burden of chronic hepatitis D, therefore we believe it would be unreasonable to characterise CHD as a non-severe condition. Failing to apply a severity weighting as a result of a fraction of patients being older is potentially discriminatory towards the large cohort (55%) of young patients diagnosed with hepatitis D who have a large unmet need.

2.2 Scenario based on mean age from UKHSA

The committee considered basing the baseline age for patients with cirrhosis on diagnosis in the UK with CHD on UKHSA data. Data on cirrhosis status were not provided by UKHSA however the mean age of all patients when they first tested positive for HDV RNA has been explored in the model by changing the baseline age to [redacted] years. Table 7 shows that the ICER (including the 1.2 severity modifier) increases from £24,061 to £24,433 noting that both analyses qualify for the 1.2 severity modifier.

Table 7: Scenario where baseline age is set to UKHSA mean vs. median

Analysis	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)*	Base-case ICER (£/QALY)†
Company	[redacted]	4.78	[redacted]	£29,320	£28,874
Company with severity modifier				£24,433	£24,061

*Average age based on UKHSA (2022) mean of [redacted] years.

†Average age based on UKHSA (2022) median of 35.0 years.

Topic 3 Progression/regression rates of combined responders

ACD section 3.9 *"Clinical experts agreed with the company that combined responders would have a low risk of progression through fibrosis stages, but argued that this would not be zero because this group could still have detectable levels of virus. They added that even combined responders may still be at risk of hepatocellular carcinoma. Clinical experts further explained that it is plausible that fibrosis regression could occur in combined responders, but added that the company's assumed transition probabilities for fibrosis regression seemed high."*

Company response:

- Including a small but non-zero risk of progression for combined responders in the model had a minor impact on the company's base case ICER.
- Reducing regression rates in the model had a more substantial impact, but given these rates of regression were informed by real-world evidence in patients with viral hepatitis, we do not consider the requested scenario analysis to be realistic.

3.1 Summary

Data from MYR 301 are currently too immature to reliably inform the impact of bulevirtide on rate of progression. However, it is reasonable to assume that a patient who has had a ≥99% (≥2-$\log_{10}$) reduction in their viral RNA load and alanine aminostransferase (ALT) normalisation will have a substantial benefit approaching zero progression if their hepatitis B infection is well controlled. However, we have carried out scenario analyses in the following sections that demonstrate that assuming a low rate of progression *relative to* virologic-only responders has a low impact on the ICER compared with the Company base case.

Similarly, the estimates for regression in the model were based on the published literature in viral hepatitis. The source informing regression from the compensated cirrhosis (CC) (F4) to F3 health states was Farci *et al.,* (2004) (8), a longitudinal study of 41 CHD patients based in Italy. Thirty-six patients with CHD who participated in a randomised controlled trial of a 48-week course of high (9 million units) or low (3 million units) doses of PEG-IFN or no treatment were followed for an additional 2 to 14 years. The mean follow-up time was 10.8 years. The regression rates in the model were

informed by the regression rates observed in patients who had sustained biochemical response in Farci *et al.,* (2004). For F3 to F2, regression rates were sourced from Marcellin *et al.,* (2013) (9), a 5-year follow-up study of HBV mono-infected patients who had been enrolled in a 48-week randomised clinical trial where they had been treated with tenofovir disoproxil fumarate (TDF) or adefovir dipivoxil. In the follow-up study, patients received treatment with TDF. Six hundred and forty-one patients were recruited from 80 different study locations including the US, Canada, France, Turkey and the UK. Five hundred and eighty-five (91%) of these patients entered the open-label phase (follow-up study) and 489 patients (76%) completed 240 weeks of the study. Regression rates in the model were informed by the proportion of patients who experienced viral suppression while on treatment with TDF.

These rates of regression are likely generalisable to a patient with CHD experiencing a combined response. We have nevertheless, as per the committee's request, carried out a scenario analysis where regression rates in the model are reduced. While this has a larger magnitude of impact on the ICER than reducing progression rates, we do not consider this to be a realistic scenario given that our original modelled estimates are obtained from real-world evidence of regression in viral hepatitis.

3.2 Progression through fibrosis stage for combined responders

The committee considered that the risk of progression through fibrosis stage for the combined responders should be low but not zero. We have explored this by assuming that progression is reduced relative to that of partial responders instead of assuming that it is zero. We have carried out an analysis where we assume that the hazard ratio for progression in combined responders is 20% of that applied to partial responders. That is, 0.08 in combined responders vs. 0.42 in partial responders for fibrosis states Fx->Fx+1 and 0.05 in combined responders vs. 0.26 in partial responders for fibrosis states F4->decompensated cirrhosis (DCC). Results are reported in Table 8.

Table 8: Scenario of progression through fibrosis stage for combined responders

Analysis	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	Base-case ICER (£/QALY)
Company	[redacted]	4.74	[redacted]	£29,434	£28,874
Company with severity modifier				£24,528	£24,061

3.3 Progression to HCC for combined responders

The committee considered that the risk of progression to hepatocellular carcinoma (HCC) for combined responders should be low but not zero. We have explored this by assuming that progression is reduced relative to that of partial responders instead of assuming that it is zero. We have carried out an analysis where we assume that the hazard ratio for progression in combined responders is 20% of that applied to partial responders. That is, 0.07 in complete responders vs. 0.34 in partial responders for all transitions to HCC. Results are reported in Table 9.

Table 9: Scenario of progression to HCC for combined responders

Analysis	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	Base-case ICER (£/QALY)
Company	[redacted]	4.71	[redacted]	£29,423	£28,874
Company with severity modifier				£24,519	£24,061

3.4 Regression in combined responders

The committee considered that the Company's assumed transition probabilities for fibrosis regression appeared high. We have explored this by carrying out an analysis where we reduced the probability of fibrosis regression for combined responders by 50% (4.41% for CC (F4) ➔ F3; and 6.65% for F3 ➔ F2 in the scenario). Results are reported in Table 10. It can be seen that the impact on the Company's base case ICER is modest, resulting in an increase of £807 however the ICER remains well below the ICER threshold of £30,000 per QALY gained.

Table 10: Scenario of regression in combined responders

Analysis	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	Base-case ICER (£/QALY)
Company	[redacted]	4.64	[redacted]	£29,841	£28,874
Company with severity modifier				£24,868	£24,061

Topic 4 Treatment duration beyond 48 weeks in MYR 301

ACD section 3.11 *"Clinical experts broadly agreed with the company's model assumptions for combined responders and non-responders but were less sure of what would happen for virological responders…Clinical experts added that treatment would also likely continue for combined or virological responders who develop hepatocellular carcinoma, and that for people with convincing evidence of virus eradication, treatment would likely be stopped.*
The committee agreed with the clinical experts' assumptions but noted that there is remaining uncertainty around whether the stopping rules assumed by the company are aligned with those used in MYR 301 until data beyond 48 weeks becomes available"

Company response:

- The Company has carried out a scenario analyses which explores the impact of continuing treatment in patients who develop HCC and relaxing the treatment continuation criteria to achievement of virologic response only.
- While assuming the same continuation rules for virologic and combined responders increases the ICER, we note that clinicians were unsure that virologic responders would have the same continuation rules and that this may only apply to specific cases.
- The more realistic scenario that patients with virus eradication could discontinue treatment substantially offsets any effect from a minority of virologic responders continuing treatment.

4.1 Summary

The Company has included a range of scenarios to explore how treatment continuation criteria impact on estimates of cost-effectiveness. These include:

- Continuing treatment with bulevirtide in patients who develop HCC.
- Assuming the same continuation rules for virologic responders as combined responders, either at Week 48 or Week 72.
- Assuming that patients with undetectable HDV RNA discontinue bulevirtide.

Continued treatment for HCC patients is a scenario previously explored by the EAG and included in their base case, with negligible impact on the ICER.

With respect to the scenarios applying the same continuation rules for virologic-only responders, we note from the ACD that clinicians appeared unsure about this assumption, and that it might apply only in specific circumstances e.g., "*if a patient had a virological response but high ALT for reasons other than hepatitis, for example fatty liver disease or alcohol use*." We therefore consider that the results of this scenario analysis represent a situation where all patients with a virological response remain on treatment.

Finally, the scenario where patients with undetectable HDV RNA discontinue treatment is a realistic one given this approach is taken for other viral hepatitis treatments. In isolation, this scenario leads to a substantial reduction in the ICER as can be seen in Table 14. Applying this clinically realistic scenario to the more unrealistic scenario that *all* virologic-only responders continue treatment substantially reduces the unfavourable impact of the latter assumption.

4.2 Treatment continuation with hepatocellular carcinoma

The committee considered that treatment should be continued for people who develop HCC. We have explored this by carrying out an analysis where we captured the cost of treatment for HCC patients in the model. Note that this was a scenario that had already previously been introduced by the EAG to which the model is insensitive. Furthermore, the Company has now adopted this as part of their new base case. For comparison purposes, we therefore compare the results of *excluding* costs of HCC patients. Table 11 shows that excluding treatment costs for patients who develop HCC has a negligible impact on the ICER which decreases from £24,061 to £24,055.

Table 11: Scenario of treatment continuation with HCC

Analysis	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)*	Base-case ICER (£/QALY)†
Company	[redacted]	4.91	[redacted]	£28,866	£28,874
Company with severity modifier				£24,055	£24,061

*Impact of no treatment costs in patients who develop HCC.

†Impact of including treatment costs in patients who develop HCC.

4.3 Treatment continuation for virologic responders

The committee considered having the same treatment continuation assumptions for virologic responders as for combined responders. We have explored this in the model by changing the response criteria in the existing model Settings sheet. That is, at Week 48 non-responders discontinue treatment but virologic responders remain on treatment without any further assessment at Week 72. We then carry out a further scenario where the assessment for non-response is instead carried out at Week 72 instead of Week 48 (which uses the model extrapolations in the Company's scenario). Results are reported in Table 12 and Table 13.

This scenario leads to the largest increase in the ICER, but we note that the committee also discussed the potential for patients with virus eradication to discontinue treatment, modelled in the next scenario. We also explore the impact of combining the present scenario with that of discontinuation of treatment with virus eradication.

Table 12: Scenario with treatment continuation for virologic responders (Week 48)

Analysis	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	Base-case ICER (£/QALY)
Company	[redacted]	3.66	[redacted]	£34,749	£28,874
Company with severity modifier				£28,957	£24,061

Table 13: Scenario with treatment continuation for virologic responders (Week 72)

Analysis	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	Base-case ICER (£/QALY)
Company	[redacted]	3.66	[redacted]	£35,198	£28,874
Company with severity modifier				£29,332	£24,061

4.4 Stopping treatment with virus eradication

The committee considered having the treatment stopped for those with convincing evidence of virus eradication. In the absence of specific feedback from clinicians regarding what constitutes "convincing evidence", we have explored this by assuming that patients with a combined response who had undetectable HDV RNA at 48 weeks discontinue treatment 52 weeks later. This is achieved by removing the costs of bulevirtide from Week 120 onward for the proportion of combined response patients with undetectable HDV RNA at 48 weeks [redacted] while maintaining them in the complete response health states. Note that this will still overpredict costs given that, for simplicity, we do not remove the costs of hepatitis D monitoring. The results of this scenario are presented in Table 14. As the Company has now incorporated this into their updated base case, for comparison purposes, we therefore compare the results of *excluding* the assumption of treatment discontinuation. It can be seen that continuing treatment for all patients increases the ICER (with severity modifier of 1.2) from £24,061 to £27,165 per QALY gained.

Table 14: Scenario of continuing treatment despite virus eradication

Analysis	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)*	Base-case ICER (£/QALY)†
Company	[redacted]	4.91	[redacted]	£32,598	£28,874
Company with severity modifier				£27,165	£24,061

*Impact of continuing treatment for all patients including those with convincing evidence of virus eradication.

†Impact of stopping treatment for patients with convincing evidence of virus eradication.

4.5 Treatment continuation for virologic responders combined with stopping treatment with virus eradication

In section 4.3 we explored changing the response criteria to virologic. That is, at Week 48 non-responders discontinue treatment but virologic responders remain on treatment without any further assessment at Week 72. Below we combine that scenario with that in section 0 where patients with virus eradication are assumed to discontinue treatment with bulevirtide. As previously, we deduct the costs of bulevirtide from Week 120 onward for the proportion of patients with undetectable HDV RNA at 48 weeks while maintaining them in the complete response health states (now assumed within our Company base case). In this scenario, the proportion of patients with undetectable RNA is [redacted], as the definition of a complete responder is virologic whereas in section 0 it was combined response. The results of this scenario are presented in Table 15.

Table 15: Scenario of treatment continuation for virologic responders combined with stopping treatment with virus eradication

Analysis	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	Base-case ICER (£/QALY)
Company	[redacted]	3.66	[redacted]	£35,198	£28,874
Company with severity modifier				£29,332	£24,061

Topic 5 The size of the utility gain for combined responders

ACD section 3.12 *"The committee was less certain about the size of the utility gain that should be applied. It noted the lack of justification for the Tobit approach and highlighted that the resulting utility gain from the regression model was not statistically significant. It recalled that in previous appraisals of hepatitis C, combined response was associated with a smaller utility gain than assumed by the company. The committee concluded that the size of the utility benefit for combined responders was uncertain."*

Company response:

- NICE methods guidance stipulates that where possible utilities from the technology's clinical trials should be used in the economic model. Our choice of regression model for generating utilities was underpinned by observed ceiling effects in the MYR 301 data.
- Utility gain for patients with sustained virologic response (SVR) in other hepatitis appraisals has been slightly lower (different by ≤0.02) than that observed for combined responders in MYR 301, however this may be explained by differences in the type of hepatitis infection and population.

5.1 Summary

The committee queried the method used for deriving the utility gain of responders from the MYR 301 data and requested a comparison with the utility values used in other relevant technology appraisals (TAs). In section 5.2 we provide more information regarding the observed ceiling effect that justifies the use of the Tobit regression model.

In section 5.3 we present the results of a literature search covering both prior NICE TAs and the published literature. The results of this search showed high heterogeneity, highlighting that utility gain can vary significantly by population sampled. The values used for SVR in other NICE TAs were broadly in line with those obtained from MYR 301 using our Tobit regression model. However, NICE methods stipulate that the preferred source of utility in an economic model is to use "*EQ-5D reported by patients/carers in a relevant study*" (10). As the MYR 301 study is the only study that

reports utility gain from the relevant population of CHD patients, then the data from MYR 301 are the appropriate values to be used in the model.

Notwithstanding this, we have explored in section 5.4 the impact of utility gain in a scenario analysis by assuming 50% or 75% of the current utility gain for responders. Results for both cases are reported in Table 18 and Table 19, in which it can be seen that this has a modest impact on the Company's base case cost-effectiveness results.

5.2 Justification for use of the Company's Tobit model for utility gain

The committee noted the lack of justification for the Company's Tobit model around median (CLAD [censored least absolute deviations] regression) approach to deriving utility gain for responders.

EuroQol 5 Dimension (EQ-5D) index scores from MYR 301 are presented in Figure 1, which show that the distribution of the EQ-5D index was significantly skewed to the left, with the peak of the histogram on the right; approximately 40-50% of the subjects obtaining the highest score. This strongly suggests that a ceiling effect was present in the data, which occurs when a high proportions of subjects in a study have maximum scores on the observed variables.

Figure 1: EQ-5D scores at Week 48 overall and treatment by arm

When data have pronounced ceiling effects, the use of ordinary least squares (OLS) regression violates the statistical requirement for linearity of conditional expectation, leading to inaccurate predictions of preference-based scores and inaccurate identification of predictor variables (11).

The Tobit model is preferable over OLS regression when a ceiling effect is present or the dependent variable is censored. The CLAD approach is based on an assumption that the median will be more robust to ceiling effects than the mean. The coefficients

are estimated so as to minimize the sum of the absolute deviations from the regression line (12, 13). The Company therefore considered that the Tobit CLAD regression comprised the most appropriate approach to deriving utility gain of responders from the MYR 301 data.

5.3 Utility gain for responders from past technology appraisals

The committee considered having alternative estimates of utility gain for combined responders, based on previous hepatitis technology appraisals (TAs). The Company has explored this issue by reviewing previous TAs in hepatitis B and C, supplemented with data from the literature by re-examining the papers retried in our health-related quality of life systematic literature review. In hepatitis B TAs, no utility gain was assumed for virologic responders who were not in SVR and patients with SVR were assumed to have a small utility decrement (1%) relative to the general population. In TAs for hepatitis C we could only identify utility gains for patients with SVR. These are provided in Table 16 below.

It can be seen that these utility gains ranged from 0.03 to 0.05. However, we note the committee's comment from TA413 that "*where available, it prefers utility values collected from the clinical trials used to inform the effectiveness of the intervention under evaluation to those estimated from other sources*." Given that the [redacted] value used in the economic model was directly from the MYR 301 trial data, it is therefore appropriate to use this value in the model as it was obtained from a hepatitis D-infected population in which combined response might not unreasonably lead to greater utility gains.

Values in the literature show high heterogeneity, ranging from 0.053 to 0.2 in various regression models (Table 17), demonstrating how much this can vary between different cohorts of patients. This variability further supports the need to utilise the utility gain from responders collected in the MYR 301 study, as it will be representative of a cohort of patients receiving treatment with bulevirtide for CHD.

Table 16: Utility gains for patients with SVR in NICE TAs

Technology Appraisal (TA)	Topic	Published date	Utility gained value	Source used
TA330	Sofosbuvir for treating chronic hepatitis C	2015	0.05	Wright *et al.*, 2006 (14)
TA363	Ledipasvir–sofosbuvir for treating chronic hepatitis C	2015	0.04	Vera-Llonch *et al.*, 2013 (15)
TA413	Elbasvir–grazoprevir for treating chronic hepatitis C	2016	0.03	European subgroup of the elbasvir–grazoprevir trials.

Table 17: Utility gains for patients with SVR in the literature

Study setting	Utility gained value	Reference
Clinical trials of sofosbuvir in patients with chronic HCV	0.043	Stepanova *et* al., 2014 (16)
Clinical trial of telaprevir combination therapy in chronic HCV	0.040	Vera-Llonch *et al.*, 2013 (15)
Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation	0.060	Wright *et al.*, 2006 (14)
Cross-sectional survey in chronic HCV patients in France	0.213	Samp *et* al., 2015 (17)
Prospective observational study, patients with chronic HCV in Spain	0.040	Juanbeltz *et al.*, 2019 (18)

5.4 Alternative scenarios for responder utility gains

The committee requested to see alternative estimates of utility gain for combined responders, based on previous hepatitis appraisals. As explained in the previous section, utility gains for patients in SVR have been in the same range as those observed for combined responders in MYR 301. However, recognizing that the patients in MYR 301 were not in SVR, we explore two scenarios where the current utility gain in the model [redacted] is reduced by 50% and 75% in Table 18 and Table 19 below. In both scenario analyses it can be seen that bulevirtide is associated with

substantially higher QALYs compared to BSC, with the Company's base case ICER being below £30,000 per QALY gained with the severity modifier.

Table 18: Scenario of assuming 50% of the current utility gain for responders

Analysis	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	Base-case ICER (£/QALY)
Company	[redacted]	4.91	[redacted]	£30,210	£28,874
Company with severity modifier				£25,175	£24,061

Table 19: Scenario of assuming 75% of the current utility gain for responders

Analysis	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	Base-case ICER (£/QALY)
Company	[redacted]	4.91	[redacted]	£29,527	£28,874
Company with severity modifier				£24,605	£24,061

Topic 6 The long-term survival for people on standard care, in the absence of bulevirtide

ACD section 3.15 *"The committee added that many of the EAG's preferred assumptions around the natural history modelling of chronic hepatitis D may also affect the severity weighting calculations because they affect QALYs accrued by people having standard care…It added that validation of the model predictions for people on standard care using external literature sources would be helpful, along with graphical representations of health state occupation over time."*

Company response:

- As requested, we have validated the progression and survival rates predicted by the economic model with those in the published CHD literature by comparing Kaplan-Meier plots with survival plots extracted from the model.
- There was close alignment between the model predictions and the published literature, with divergence only observed at later timepoints where costs and outcomes are discounted

6.1 Summary

The committee requested validation of the predictions of disease progression for patients on best supportive care from the economic model using the external published literature. The Company has carried this out for a number of model transitions, including those to more severe fibrosis states, to HCC and for overall survival. It can be seen from the superimposed Kaplan-Meier/survival plots that the model predictions align closely with those observed in the CHD literature, with the curve shapes only diverging at later timepoints. This is likely a feature of time-changing hazards of progression and death in the real-world, whereas the model uses constant transition probabilities conditional on response. Introducing time-dependent transition probabilities would require substantial reworking of the model and increase model complexity. Furthermore, in many cases divergence from the observed data only occurred after many years, by which time outcomes in the model are highly discounted and thus less likely to impact the ICER.

We have furthermore, in section 6.3, produced plots of model health-state occupancy over time as well as an overall survival plot for the two arms to facilitate decision-making.

6.2 Progression/survival rates in the CHD literature

The validation of the long-term survival for people on BSC in the absence of bulevirtide was conducted based on the following factors:

1. Availability of Kaplan-Meier survival data on HDV.
2. Availability of information on granular fibrosis stages and/or data specific to compensated cirrhosis patients.
3. Data specific to untreated patients or patients without treatment response (as these would be assumed to be most similar to BSC patients in the model).

Kaplan-Meier curves from the selected natural history studies were digitized using the program Plot Digitizer. Baseline demographics (e.g., baseline fibrosis distribution, patient age, sex distribution) were aligned with the natural history studies based on available data. In several studies, fibrosis stage data were only available for compensated cirrhotic (F4) vs. non-cirrhotic (F0-F3) health states. In these cases, the relative distribution of patients across F0-F3 was based on Romeo *et al.,* (2009) (19). Model outcomes for advanced liver-disease events were compared against the digitized Kaplan-Meier curves from these natural history studies based on visual inspection. We have explored this in several studies, described in detail below.

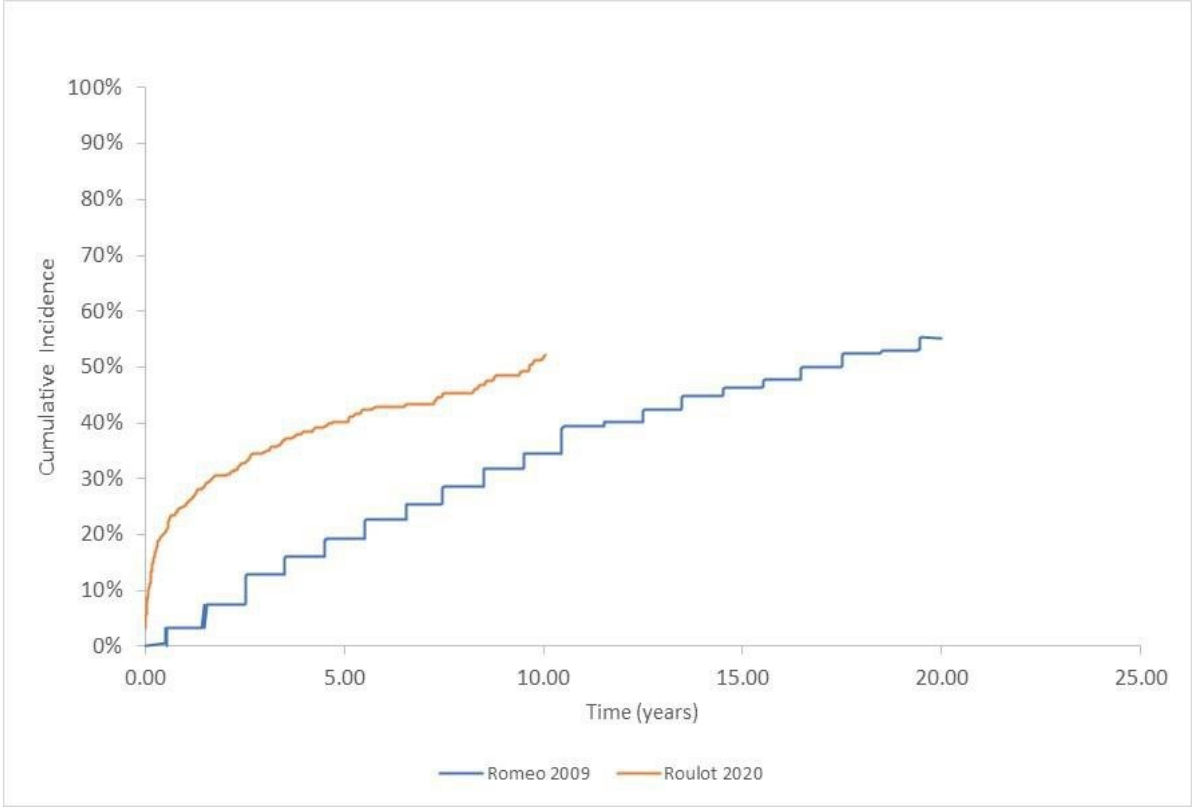
6.2.1 Compensated cirrhosis

Given the availability of granular information regarding the distribution of patients from F0-F4 health states in the Romeo *et al.,* (2009) study, this study was selected for the validation of the economic model outcomes as compared to HDV natural history. In Romeo et al., 2009, the cumulative probability of cirrhosis at 20 years was 55% with an incidence rate of 4% per year in the overall (F0-F3) non-cirrhotic patients (Figure 1) (19). Given that the values were not reported granularly (i.e., F2-F3, F3-F4), individual transition probabilities could not be derived.

Notably, these estimates from Romeo *et al.,* (2009) may even be conservative, as the Roulot *et al.,* (2020) study of a French retrospective cohort of HDV patients estimated

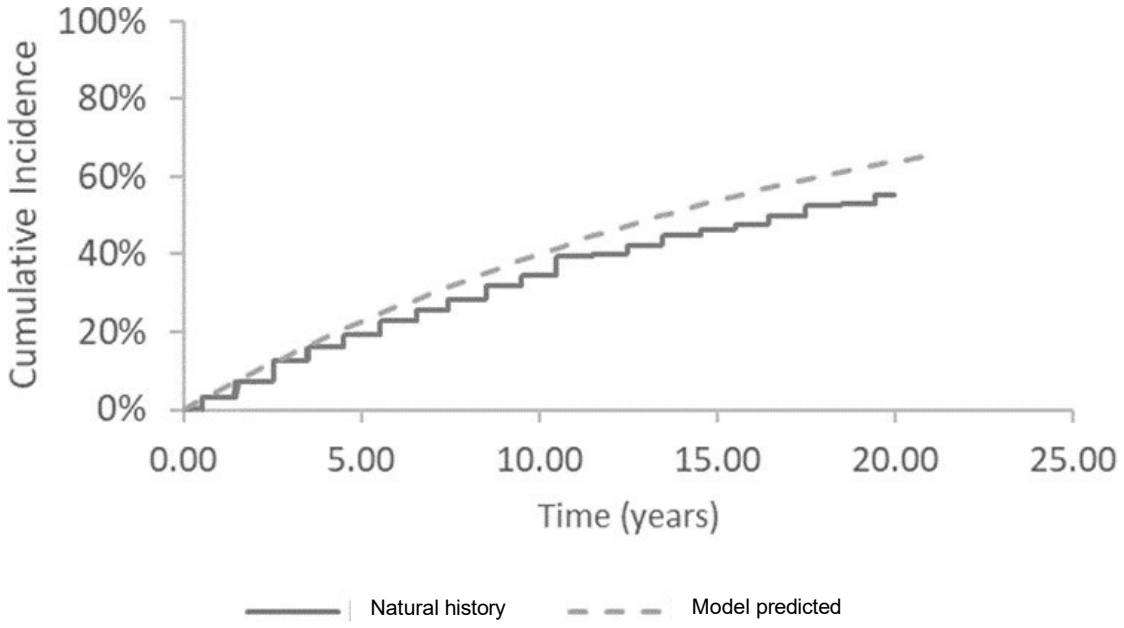
a 5-year risk of cirrhosis of 49.4% in non-cirrhotic patients (notably including both treated and untreated patients; Figure 2) (20). Further, in this study, where 407 (36.6%) patients had significant or severe fibrosis (i.e., METAVIR score ≥F2) at baseline, among new cirrhotic patients after a median follow-up of 3.0 years, 166 out of 174 (95.4%) patients had been classified as having METAVIR score ≥F2 at referral (20). These data support a fast rate of progression in patients with late-stage fibrosis.

Figure 2: Cumulative incidence of compensated cirrhosis in Romeo *et al.,* (2009) and Roulot *et al*., (2002) studies



As shown in Figure 3 below, the model predictions for the incidence of compensated cirrhosis amongst the patients who are F0-F3 at model start is generally in alignment with findings from the Romeo *et al*., (2009) study. The incidence is slightly higher overall which may be supported given the results observed in Roulot *et al*., (2020) (20).

Figure 3: Cumulative incidence of compensated cirrhosis in Romeo 2009 and model Romeo predicted 2002 studies



6.2.2 Decompensated cirrhosis

In the Kamal *et* al., (2020) study, 337 patients with anti-HDV positivity, including 233 patients with HDV RNA viremia were retrospectively studied with a mean follow-up time of 6.5 years (range 0.5-33.1). In patients with HDV RNA positivity, 29.6% of patients had liver cirrhosis at baseline. 39.1% of patients with HDV RNA positivity and cirrhosis at baseline experienced hepatic decompensation and 3% of patients with HDV RNA positivity and without cirrhosis at baseline experienced hepatic decompensation (21). Cumulative decompensation-free survival is shown below in Figure 4.

Predictions from the model are similar to those from the Kamal *et* al., (2020) study (Figure 5) (21). Further, the rate of hepatic decompensation in patients with cirrhosis at baseline was 10.2% per person-year, similar to the rate estimated for use in the economic model (10.67%).

Figure 4: Kaplan-Meier decompensation-free survival curves based on HDV RNA status from Kamal *et al*., (2020)

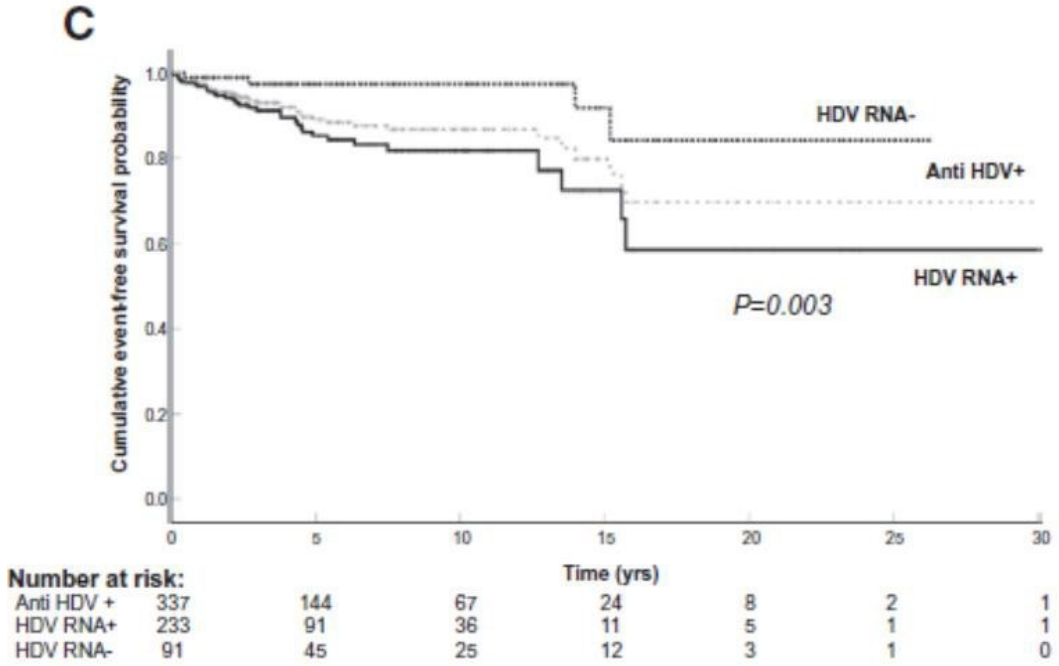
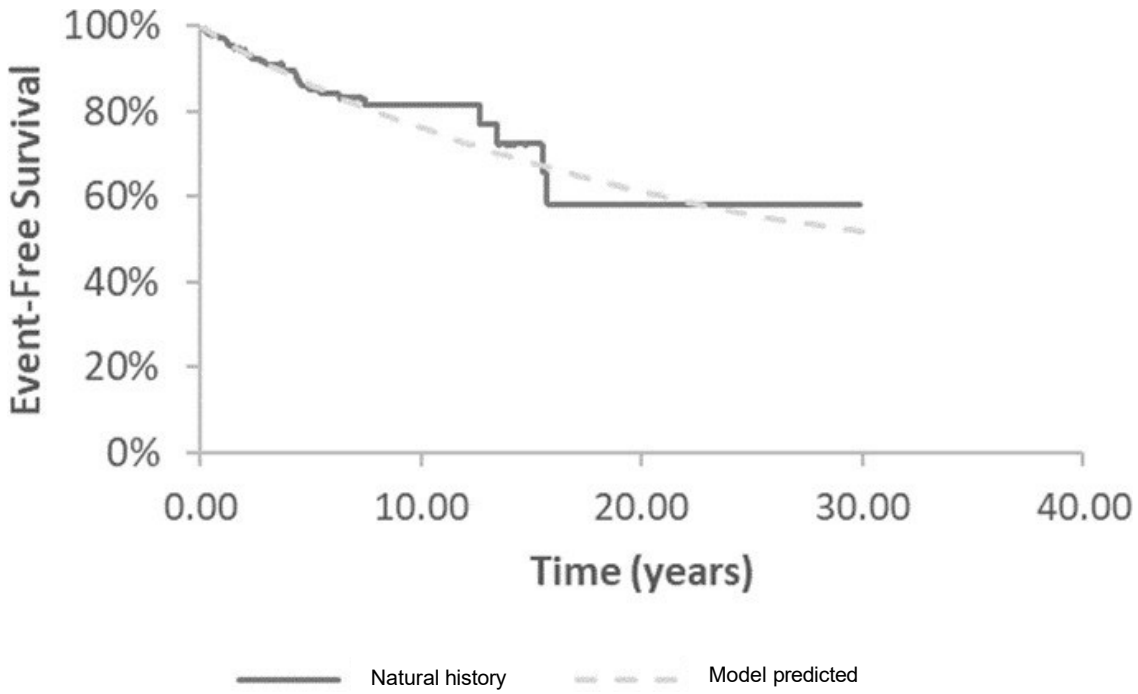


Figure 5: Comparison of decompensation-free survival of patients from Kamal *et al*., (2020) vs. predictions from economic model



6.2.3 Hepatocellular carcinoma (HCC)

In the Yurdaydin *et al.,* (2018) study, a hepatitis delta database was analysed for the effects of treatment duration on virologic response and clinical outcomes. 99 chronic hepatitis delta patients who received at least 6 months of interferon treatment were selected. Post-treatment median follow-up was 55 months (24-225 months). Of these patients, 35 achieved a maintained virologic response (MVR). In the non-responder patients, 22% (14/64) had cirrhosis present at baseline. HCC-free survival outcomes for patients without MVR, assumed to be most appropriate for comparison with BSC, are shown in Figure 6.

Given the lack of data regarding the distribution of patients from F0-F3, a similar distribution of non-cirrhotic patients was assumed based on data from Romeo *et al*., (2009) (19). The model showed generally similar results for the cumulative incidence of hepatocellular carcinoma for BSC compared to those without MVR from the Yurdaydin *et* al., (2018) study (Figure 7) (22).

Figure 6: Kaplan-Meier hepatocellular carcinoma-free survival curve from Yurdaydin *et al.*, (2018) in patients with and without MVR

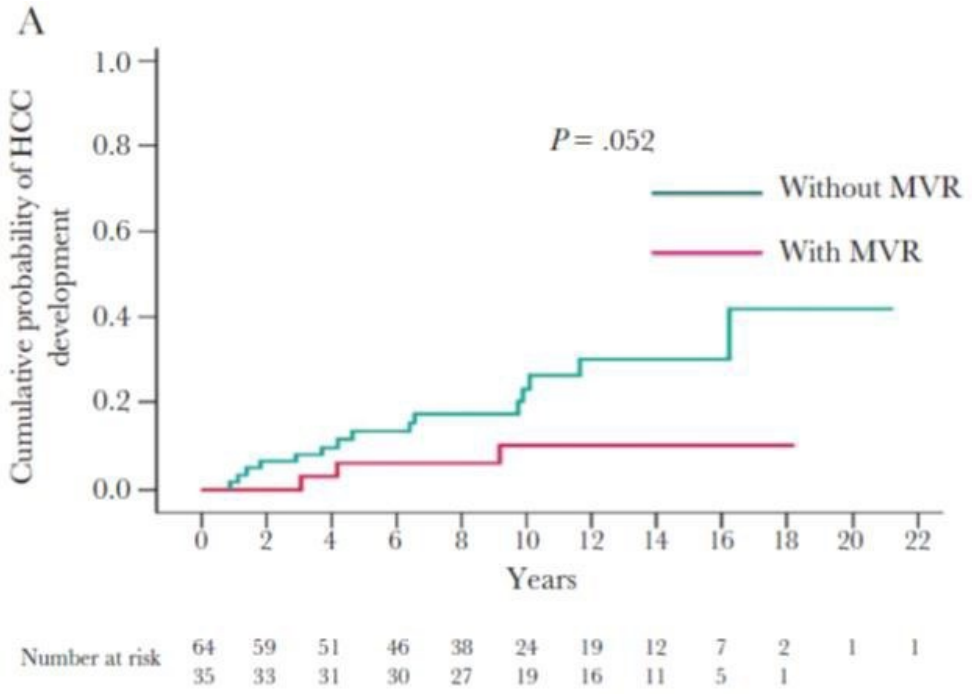
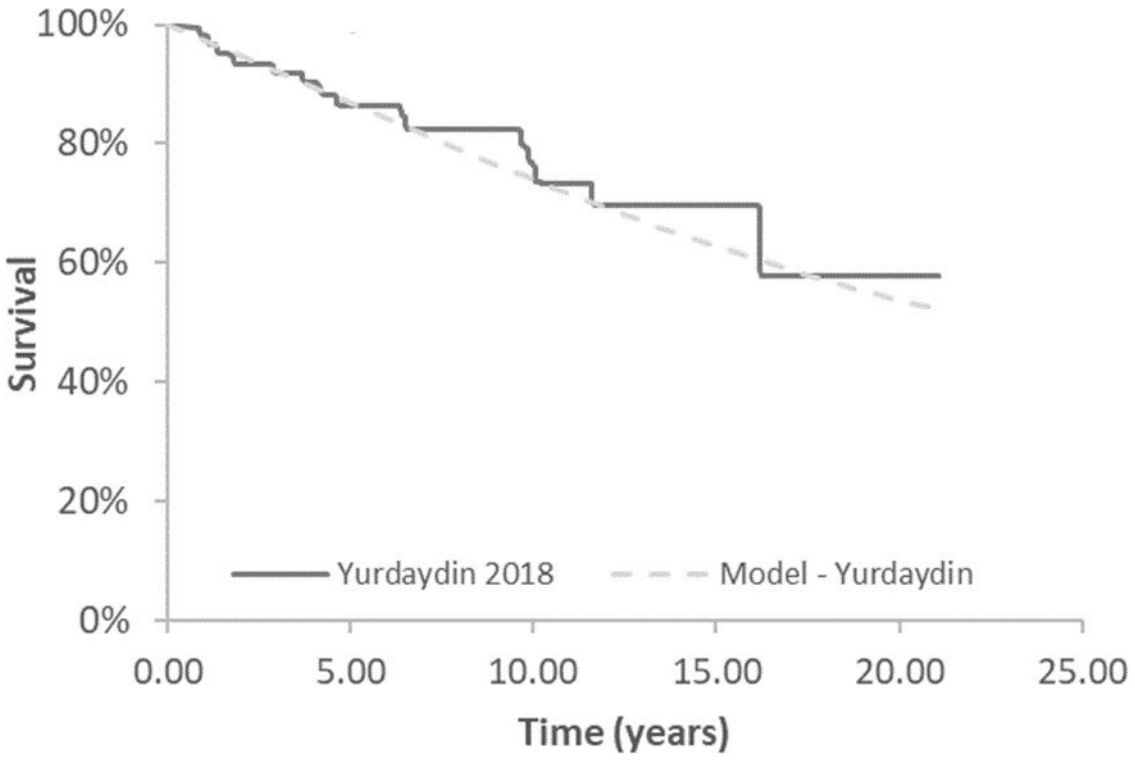


Figure 7: Comparison of survival of patients from Yurdaydin *et al*., (2018) vs. predictions from economic model



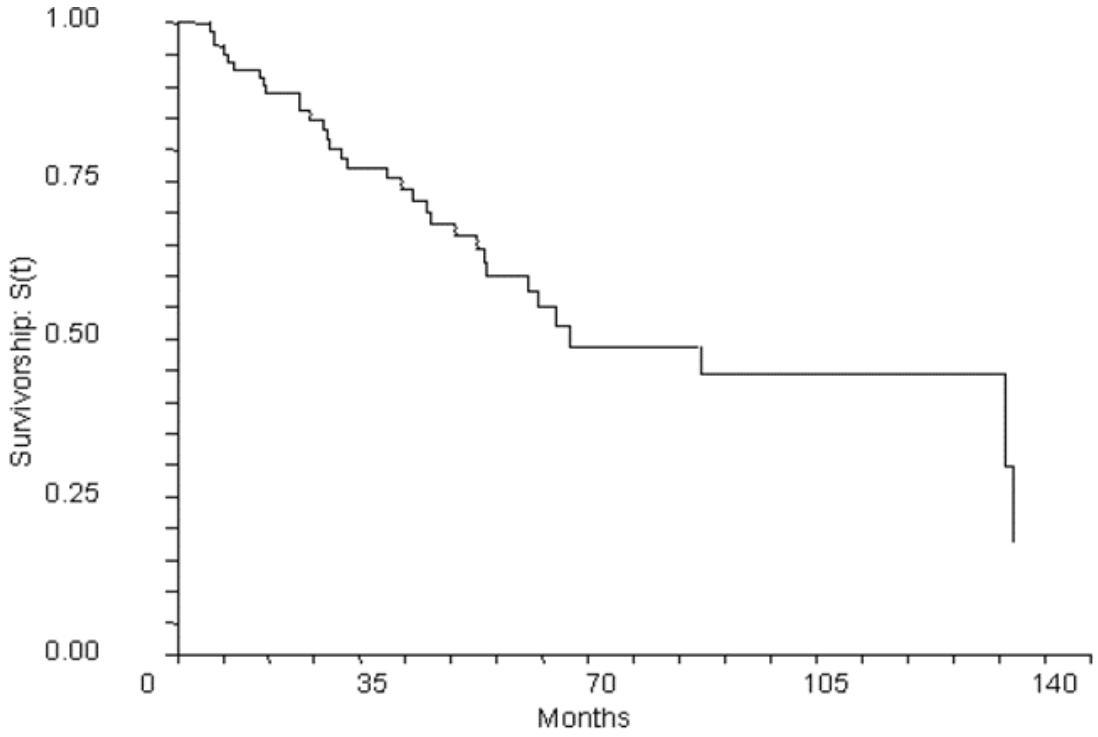
6.2.4 Liver-related mortality

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

6.2.4.1 Survival of compensated cirrh*osis (F4) patients*

The first study included 166 patients with compensated HDV-related cirrhosis diagnosed since 1994 and followed until death or 31st December 2004. Patients had a mean age of 40.7±7.9 years. The median survival was 58.3 months since the diagnosis of compensated cirrhosis, with a probability of survival after the diagnosis of compensated cirrhosis of 94.3%, 82.5%, and 51.5% at 1, 2, and 5 years, respectively (Figure 8) (23). Predictions from a purely compensated cirrhotic (i.e., 100% F4) population in the model demonstrated strong alignment with those projected from this study (Figure 9).

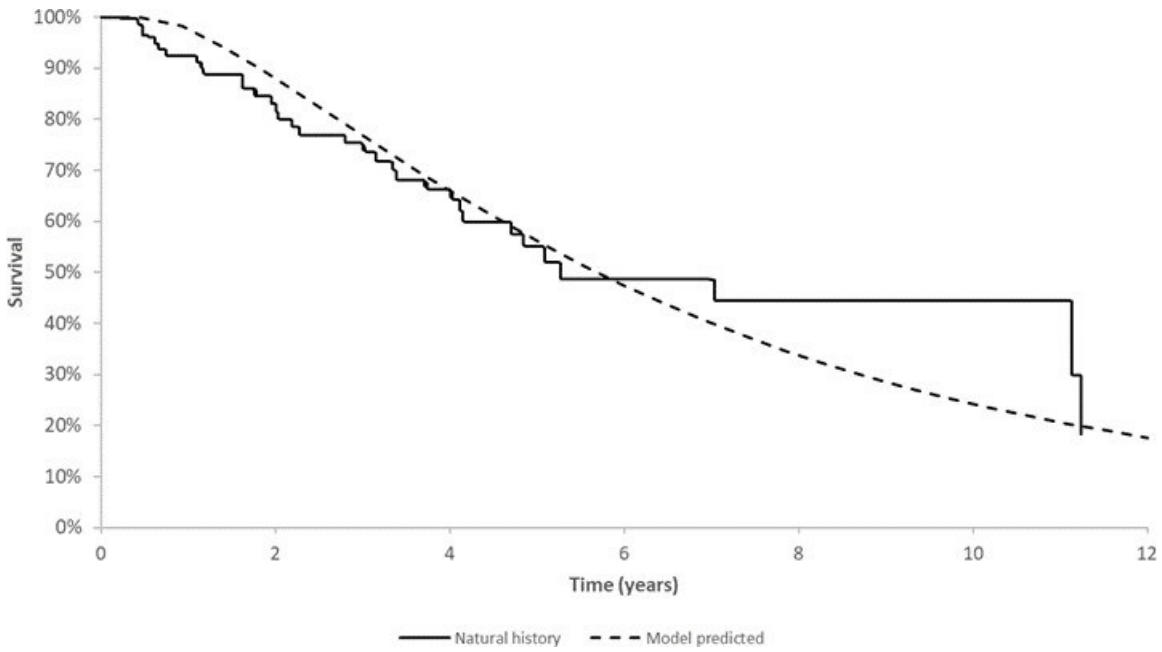
Figure 8: Kaplan-Meier survival curve of patients with compensated HBV-HDV cirrhosis from Gheorge *et al*., (2005)



6.2.4.2 Survival in broad F0-F4 population

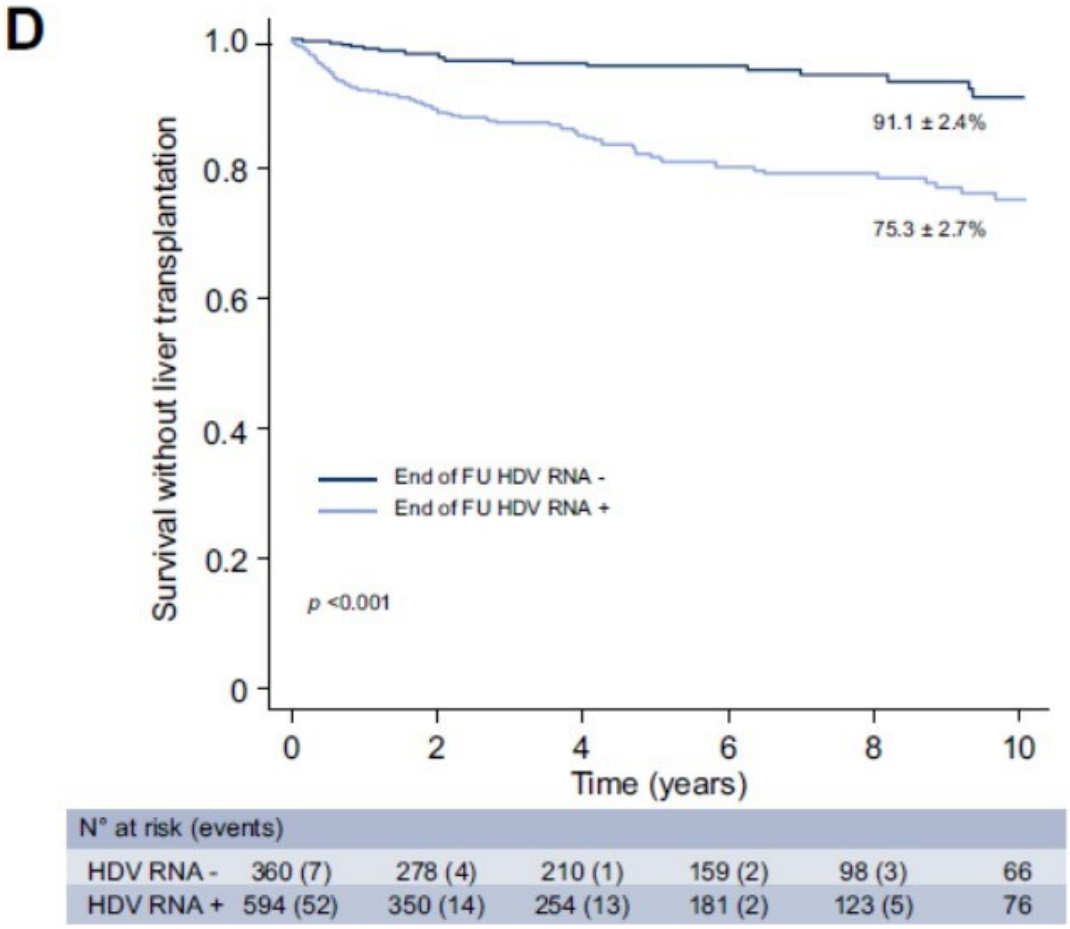
To determine whether projections from the combined non-cirrhotic and cirrhotic populations aligned with natural history studies regarding mortality, two studies were selected based on availability of data for patients without HDV RNA - (Roulot *et* al., 2020) and for those without MVR due to treatment (Yurdaydin *et al*., 2018) (20, 22).

Figure 9: Comparison of survival of compensated cirrhosis patients from Gheorge *et al*., (2005) vs. predictions from economic model



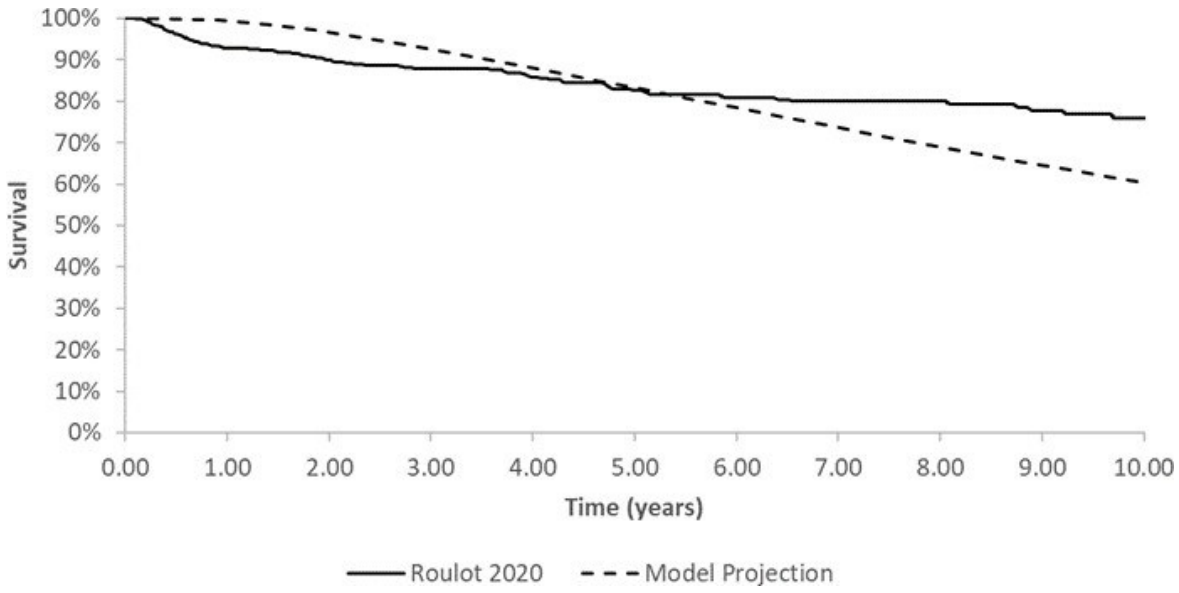
In the Roulot *et* al., (2020) study, at referral, 28.1% of patients had cirrhosis, 36.6% had significant or severe fibrosis (≥F2), and 16.8% had no or minimal fibrosis (F0-F1). The 5-year risk of death in the entire population, including patients who may have received treatment, was 20.2%. Survival according to HDV RNA status at the end of follow-up showed that patients with positive HDV viral load had a higher chance of death (hazard ratio 3.30, p<0.001; Figure 10). Projections from the model are generally similar to those from the Roulot *et* al, (2020) study, though a low number of events towards the end of follow-up creates uncertainty about survival outcomes beyond 8 years (Figure 11).

Figure 10: Survival without liver transplantation according to persistent HDV viremia before endpoint from Roulot *et al*., (2020)



N° at risk (events)						
HDV RNA -	360 (7)	278 (4)	210 (1)	159 (2)	98 (3)	66
HDV RNA +	594 (52)	350 (14)	254 (13)	181 (2)	123 (5)	76

Figure 11: Comparison of survival of F0-F4 HDV RNA+ patients from Roulot *et al*., (2020) vs. predictions from economic model



Survival outcomes in the Yurdaydin *et al*., (2018) study, for patients without MVR, assumed to be the most appropriate for comparison with BSC, are shown in Figure 12.

Given the lack of data regarding the distribution of patients from F0-F3, a similar distribution of non-cirrhotic patients was assumed based on Romeo *et al.*, (2009). Given the relatively low number of observations (Figure 12) after 10 years, these first ten years were analysed to compare model survival outcomes vs. the study. The model showed generally similar results for liver-related mortality for BSC compared to those without MVR from the Yurdaydin *et al*., (2018) study (Figure 13).

Figure 12: Liver-related mortality stratified by MVR status in Yurdaydin *et* al., (2018)

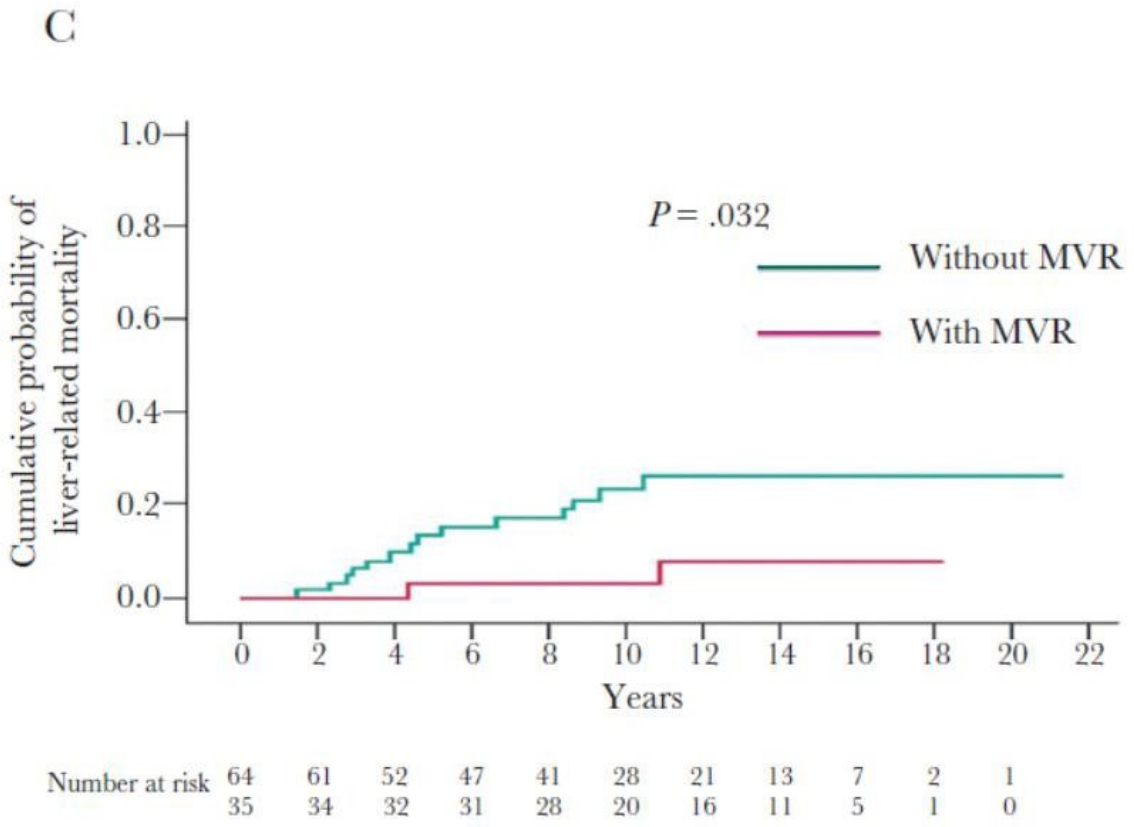
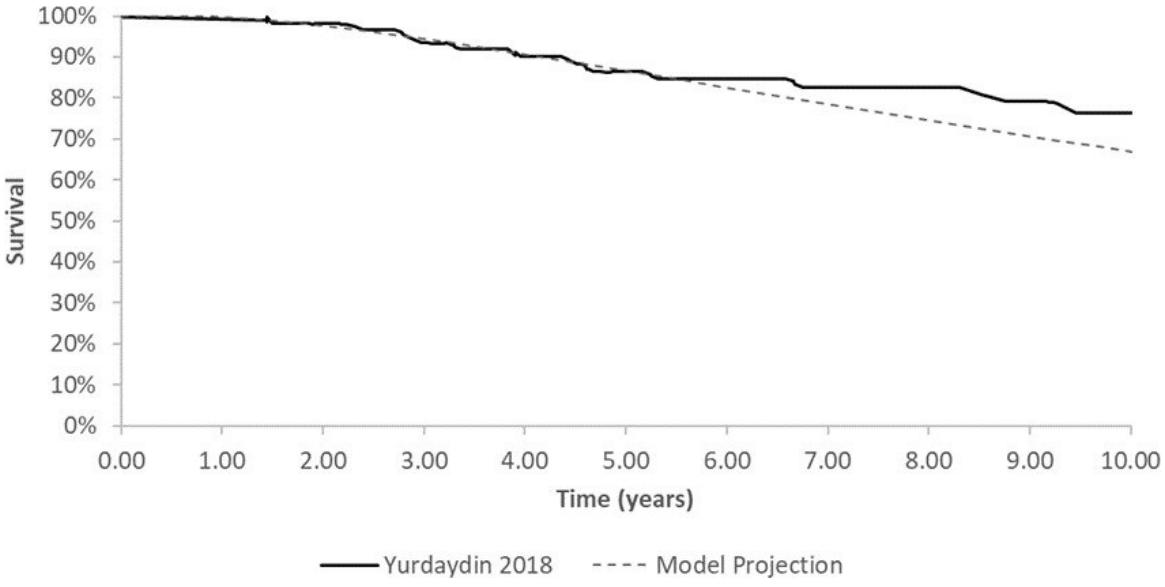


Figure 13: Comparison of survival of F0-F4 patients without MVR vs. predictions from economic model



6.3 Health state occupancy

The committee requested graphical representations of fibrosis health state occupation over time from the economic model. We have created these graphs for both arms, in addition to a graph which shows the survival over the time horizon. Results are reported in Figure 14 to Figure 16. These can also be found in the RESULTS sheet of the executable model.

Figure 14: Health state occupancy, Bulevirtide arm

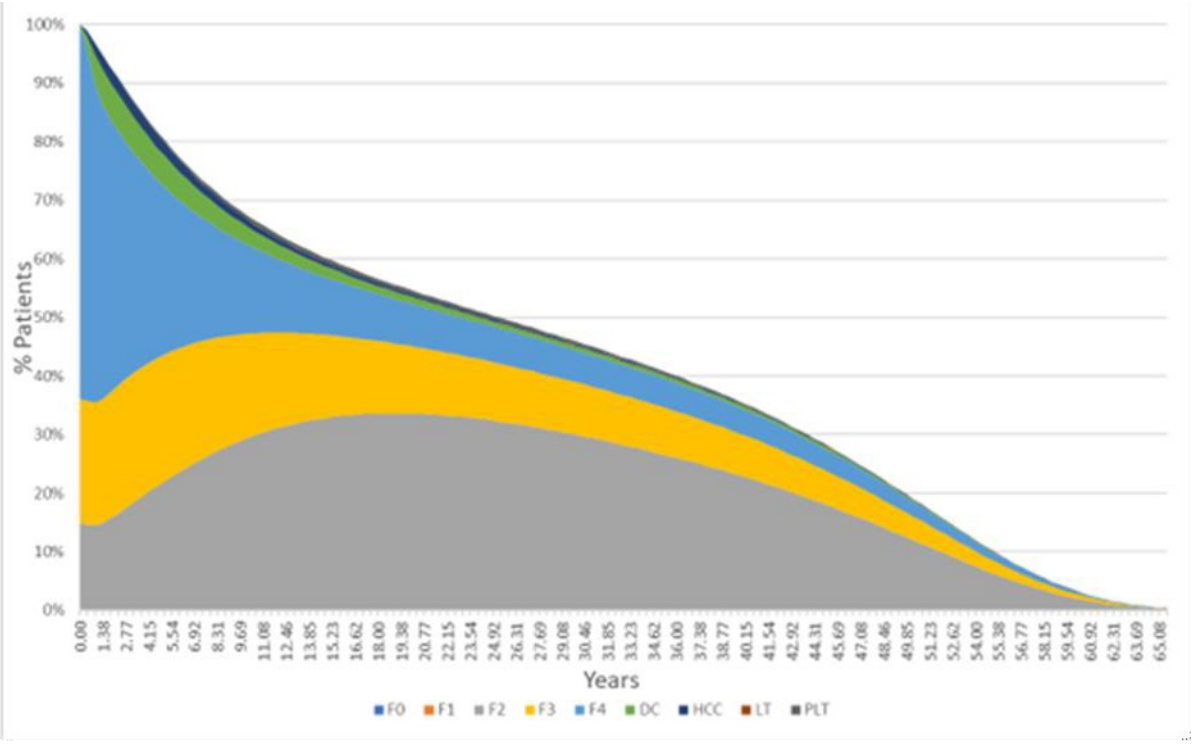


Figure 15: Health state occupancy, BSC arm

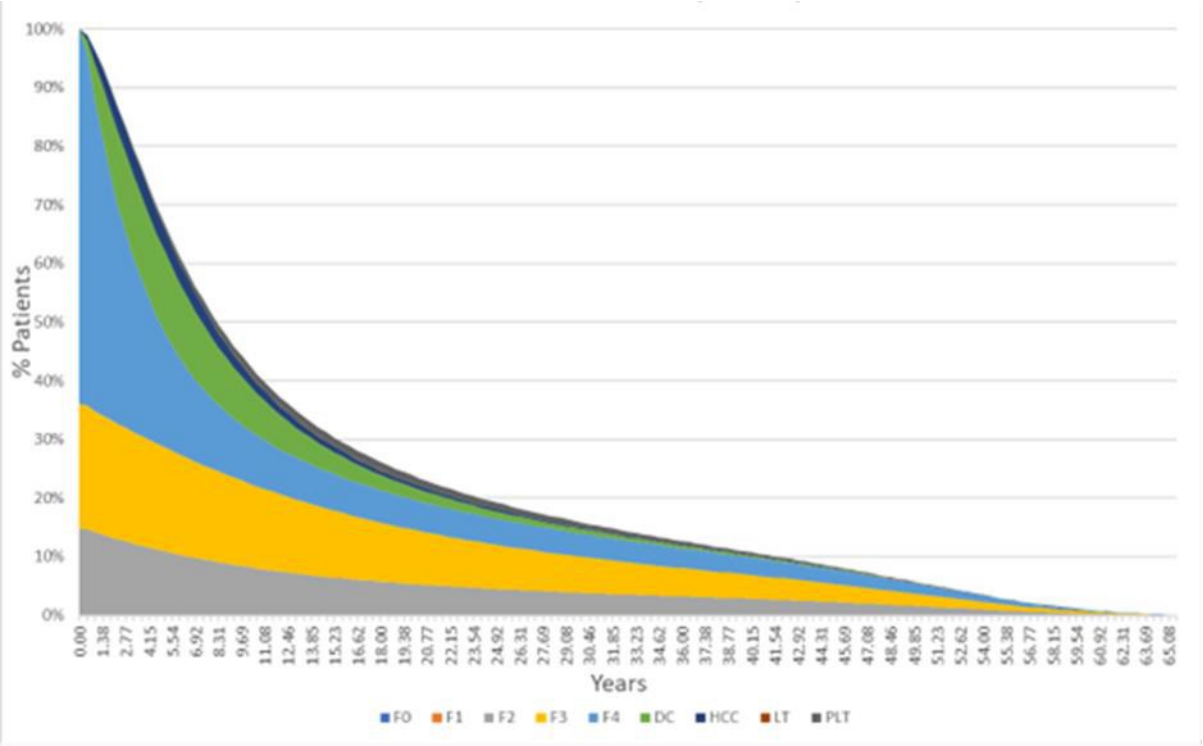
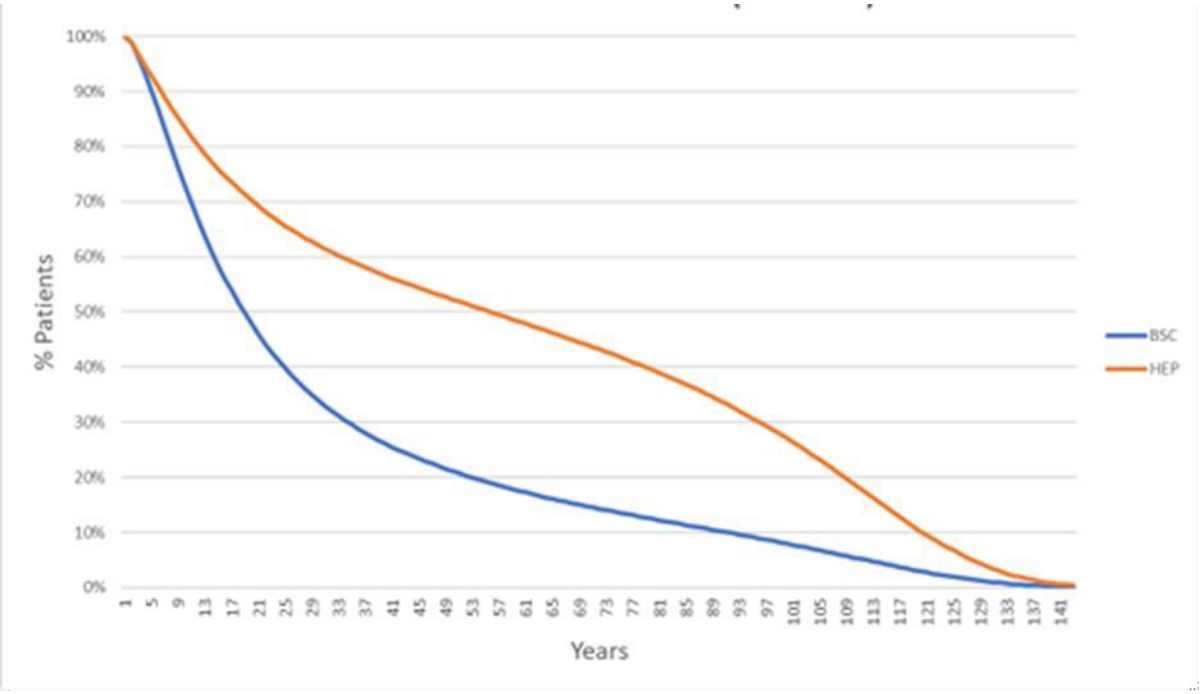


Figure 16: Overall survival



References

1. 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. 2020;72(6):1097-104.

2. UK Health Security Agency. Mean age of HDV RNA positive patients at baseline. Data on File.

3. National Institute for Health and Care Excellence. Hepatitis B (chronic): diagnosis and management. 2013 26 June 2013.

4. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis - 2021 update. J Hepatol. 2021;75(3):659-89.

5. Li Y, Huang YS, Wang ZZ, Yang ZR, Sun F, Zhan SY, et al. Systematic review with meta-analysis: the diagnostic accuracy of transient elastography for the staging of liver fibrosis in patients with chronic hepatitis B. Aliment Pharmacol Ther. 2016;43(4):458-69.

6. Qi X, An M, Wu T, Jiang D, Peng M, Wang W, et al. Transient Elastography for Significant Liver Fibrosis and Cirrhosis in Chronic Hepatitis B: A Meta-Analysis. Can J Gastroenterol Hepatol. 2018;2018:3406789.

7. 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. 2018;67(4):1560-99.

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

9. 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. 2013;381(9865):468-75.

10. National Institute for Health and Care Excellence. Centre for Health Technology Evaluation (CHTE) Methods Review: Health-Related Quality of Life. 2020.

11. Kennedy P. Guide to Econometrics. Cambridge MA: MIT Press; 1998.

12. Arabmazar A, Schmidt P. Further evidence on the robustness of the Tobit estimator to heteroskedasticity. Journal of Econometrics. 1981;17(2):253-8.

13. Johnston J. Econometrics Methods. New York: McGraw-Hill; 1997.

14. Wright M, Grieve R, Roberts J, Main J, Thomas HC. Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation. Health Technol Assess. 2006;10(21):1-113, iii.

15. Vera-Llonch M, Martin M, Aggarwal J, Donepudi M, Bayliss M, Goss T, et al. Health-related quality of life in genotype 1 treatment-naive chronic hepatitis C patients receiving telaprevir combination treatment in the ADVANCE study. Aliment Pharmacol Ther. 2013;38(2):124-33.

16. Stepanova M, Nader F, Cure S, Bourhis F, Hunt S, Younossi ZM. Patients' preferences and health utility assessment with SF-6D and EQ-5D in patients with chronic hepatitis C treated with sofosbuvir regimens. Aliment Pharmacol Ther. 2014;40(6):676-85.

17. Samp JC, Perry R, Piercy J, Wood R, Baran RW. Patient health utility, work productivity, and lifestyle impairment in chronic hepatitis C patients in France. Clin Res Hepatol Gastroenterol. 2015;39(3):307-14.

18. Juanbeltz R, Goñi-Esarte S, Martínez-Baz I, San Miguel R, Zozaya J, Rivero M, et al. 1ISG-001 Health utilities in chronic hepatitis C patients one year after successful treatment with direct-acting antivirals. European Journal of Hospital Pharmacy. 2019;26.

19. 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 Delta infection: a risk factor for cirrhosis and hepatocellular carcinoma. Gastroenterology. 2009;136(5):1629-38.

20. 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. 2020;73(5):1046-62.

21. 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(4):1177-90.

22. Yurdaydin C, Keskin O, Kalkan Ç, Karakaya F, Çalişkan A, Kabaçam G, et al. Interferon Treatment Duration in Patients With Chronic Delta Hepatitis and its Effect on the Natural Course of the Disease. The Journal of Infectious Diseases. 2018;217(8):1184-92.

23. Gheorghe L, Iacob S, Simionov I, Vadan R, Gheorghe C, Iacob R, et al. Natural history of compensated viral B and D cirrhosis. Rom J Gastroenterol. 2005;14(4):329-35.

NICE National Institute for Health and Care Excellence

Bulevirtide for treating chronic hepatitis D [ID3732]

Consultation on the appraisal consultation document – deadline for comments 5pm on 25 November 2022. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	NHS England
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	I have previously received speaker honoraria and sponsorship to attend academic conferences from Gilead but none were within the last 5 years.
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Bulevirtide for treating chronic hepatitis D [ID3732]

Consultation on the appraisal consultation document – deadline for comments 5pm on 25 November 2022. Please submit via NICE Docs.

	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We have reviewed the draft guidance and committee papers. We agree the scope of the review included the relevant evidence.
2	The summaries provided reasonable reviews of the current evidence on the use of bulevirtide for the treatment of hepatitis delta infection.
3	We agree there is a need for some further clarification in the submitted application, particularly in relation to (a) selection of patients using non-invasive fibrosis tests, (b) positioning as a primary therapy or purely for those intolerant / unresponsive to interferon and (c) duration of therapy and stopping rules.
4	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, 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 our consultations 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.

Please return to: **NICE DOCS**

Bulevirtide for treating chronic hepatitis D

Review of the company's response

January 2023

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 EAG's review of the company's response.

2 Company updated results

The company updated the patient access scheme (PAS) discount for bulevirtide from [redacted] to [redacted]. The company maintained its view that the severity modifier of 1.2 should be used in the base case analysis. Additionally, the company made the following changes to their base case analysis (in relation to the base case results presented at the second Appraisal Committee Meeting [ACM]):

1. The response rates in the model were changed to reflect those of the subgroup of patients from MYR301 with a FibroScan® score greater than or equal to 8 kPa.
2. The baseline age in the model was updated to 37 years as per the UKHSA study.
3. Combined responders (CR) were assumed to be at risk of developing hepatocellular carcinoma (HCC), estimated as 20% of that assumed for partial responders (PRs).
4. It was assumed that CRs had a probability of experiencing fibrosis progression, estimated as 20% of that assumed for PRs.
5. It was assumed that 30% of patients with HCC will be cured and accrue a utility of 0.81 afterwards.
6. The company reports assuming that CR and PRs have the same probability of developing HCC.
7. Assuming that fibrosis regression only starts occurring from cycle 4 onwards (i.e. 96 weeks) in the model.
8. Assuming that the baseline proportion of patients with METAVIR fibrosis stage F4 is 47 (based on MYR301 data) and aggregating the baseline proportion of patients in the F2 and F3 states (53% of patients) occupying these health state at baseline.
9. Assuming a utility gain of 0.05 for CR vs PR and non-responders (NRs), as per TA330.

The company's updated deterministic ICER is reported in Table 1. As the company did not provide an updated model with its response, the EAG used the previous (most recent) version of the company's model in order to try to replicate and validate the company's updated results. The EAG could not fully replicate the company's updated base case ICER in the previous version of the model. The company's updated base case ICER without the severity weighting is £29,083 (whereas the EAG-reproduced ICER in the company's previous model is £29,086), and the ICER with a 1.2. severity

weighting included is £24,236 (whereas the EAG-reproduced ICER in the company's model is £24,238). The biggest uncertainty in the company's implementation of their updated base case assumptions is around the use of the baseline distribution of fibrosis in the model (as discussed in Table 2).

In Table 2, the EAG summarises the changes made by the company in the economic model after the second ACM, together with the EAG's critique of the latter.

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]	£29,083	£24,236

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. Changes in company's model post second ACM

New assumption in company's base case results	EAG critique	Committee's preference at second ACM?	Included in EAG's preferred assumptions?
1. The response rates in the model were changed to reflect those of the subgroup of patients from MYR301 with a FibroScan® score greater than or equal to 8 kPa.	FibroScan® is not very accurate in diagnosing significant fibrosis (equivalent of METAVIR ≥F2); however, it is likely what will be used to identify patients eligible for bulevirtide in clinical practice. Of the two cut-offs put forward by the company, 8.0 kPa is likely to align more with METAVIR F3 and a cut-off of 7.25 kPa is likely to be closer to METAVIR F2. However, response data from MYR 301 using either of these cut-offs are similar to the results of the full trial population. As the inclusion of patients without significant fibrosis (METAVIR F0 or F1) has limited impact on the efficacy, the EAG prefers to use the full trial population which is more methodologically robust than the *post hoc* subgroup that breaks randomisation.	No (committee preference is for METAVIR stage ≥F2 to align with CG165)	The EAG preferred assumption remains to use the response data for the full trial population over either of the suggested subgroups.
2. The baseline age in the model was updated to 37 years as per the UKHSA study.	The EAG disagrees with the company's implementation of this assumption in the model as the company assumed the baseline age to be 36.9 (mean age in the currently alive cohort in the UKHSA dataset, N=570) instead of 37.4 years (mean age in the overall UKHSA dataset, N=620).	Yes (however not specified if preference was 37.4 or 36.9 years)	Yes, however the EAG preference is to use the mean age reported for the full dataset available in the UKHSA study (37.4 years).
3. Assumed that CRs had a probability of developing HCC, estimated as 20% of that assumed for PRs.	The EAG is unclear if the company intended to assume that CRs had a lower probability of developing HCC than PRs (20% of the probability of PRs); or alternatively; if the company intended to assume (as described in bullet point 6) that CRs and PRs have the same probability of developing HCC. Even though these assumptions are clearly contradictory, when the EAG attempted to replicate the company's updated analysis, it seemed that these have both been selected in the economic model. This resulted in an implementation in the error in the model where bulevirtide CRs have 20% of the probability of bulevirtide PRs of developing HCC, while BSC CRs have the same probability as BSC PRs of developing HCC.	Unclear. The committee agreed with the clinical experts that combined responders would still be at risk of HCC. The committee noted that the EAG assumed a residual risk of HCC in its base case and preferred to align with the EAG's assumption on this. The EAG notes that the assumption included in its base case was that CRs and PRs have the same probability of	No. The EAG preferred assumption remains that of assuming that CRs and PRs have the same probability of developing HCC. This is a conservative assumption based on the Alfaiate study suggesting that HCC is likely to occur even in patients considered to be complete responders (as discussed in the EAG original report).

		developing HCC (and not 20% as in the company's scenario).	
4. Assumed that CRs had a probability of experiencing fibrosis progression, estimated as 20% of that assumed for PRs.	When the EAG attempted to replicate the company's updated analysis, it seemed that this scenario resulted in an implementation in the error in the model where bulevirtide CRs have 20% of the probability of bulevirtide PRs of having fibrosis progression while BSC CRs have a 0% probability of progressing.	Yes. Clinical experts at committee noted that CRs could still experience a low risk of progression through fibrosis stages.	Yes. Given the committee's conclusion that CRs can still experience fibrosis progression the EAG corrected the implementation of this scenario in the model and included it in its preferred assumptions.
5. Assumed that 30% of patients with HCC will be cured and accrue a utility of 0.81.	EAG is satisfied with the implementation in the model.	Yes	Yes
6. Combined and partial responders have the same probability of developing HCC	Please see bullet point 3.	Please see bullet point 3.	Yes. Please see bullet point 3.
7. Assuming that fibrosis regression only starts occurring from cycle 4 onwards (i.e. 96 weeks) in the model	EAG is satisfied with the implementation in the model.	Yes	Yes
8. Assuming that the baseline proportion of patients with METAVIR fibrosis stage F4 is 47% at baseline (based on MYR301) and aggregating the baseline proportion of patients in the F2 and F3 states (53% of patients) occupying this health state at baseline.	The EAG is unclear on how the company implemented this in the model, particularly for the assumptions around the baseline distribution of patients in the F2 and F3 states. The EAG-preferred assumption (as discussed in the EAG original report) was to use the 47% estimate from MYR301 for the F4 state and to assume that 22% and 31% of patients were in the F2 and F3 states at baseline, respectively. The company describes their approach as "aggregating 53% of patients in the F2 and F3 states" which the EAG does not fully understand and could not replicate in the economic model. Finally, the EAG notes that when the EAG-preferred fibrosis distribution at baseline is used in the model, the	The committee agreed with the use of the MYR301 baseline distribution of fibrosis.	No. As discussed in the EAG original report, the MYR301 study only reported the baseline distribution of patients in the F4 state (47%) or below (53%) but did not provide the baseline split between patients in the F2 and F3 states. Therefore, the EAG used the Romeo *et at.* distribution at baseline, re-weighted by the 53% of patients

	ICER differs from that presented by the company in their updated base case.		in the F2 and F3 states at baseline in MYR301.
9. Assuming a utility gain of 0.05 for CR vs PR and non-responders (NRs), as per TA330.	EAG is satisfied with the implementation in the model. The company chose the 0.05 utility value which is the highest estimate reported in previous TAs.	The committee preferred the EAG scenarios incorporating the maximum utility gain for combined responders from previous technology appraisals.	Yes. Given the committee's preference for the highest utility value associated with a complete response, the EAG incorporated the 0.05 value in its base case.

3 EAG preferred assumptions

Table 3 reports the EAG's deterministic ICERs, including all EAG's preferred assumptions (as detailed in Table 1). The EAG notes that some of the EAG-preferred assumptions were not incorporated by the company in their update dbase case. These were the following:

- 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 EAG report.
- 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 EAG report.

These changes, in combination with the ones reported in Table 1, are included in the ICER reported in Table 3 and Table 4, for the deterministic, and probabilistic ICERs. The results include the company's updated PAS.

The EAG-preferred deterministic ICER amounts to £36,027. The EAG notes that the economic results are not eligible for the use of a severity weighting given that with a baseline age of 37 years, the total QALYs associated with BSC would have to be below 6.6 in order for the severity weighting to be above 1.

Finally, the EAG notes that all the ICERs herein provided remain highly uncertain with regards to the duration of treatment response and duration of treatment in the economic model. 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 then discontinue treatment (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.

Crucially, the EAG notes that the 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. At the second ACM, the committee, "*recognised there remained some ambiguity in how long treatment should continue treatment and when people who do not respond to treatment should stop having bulevirtide*[…] *The committee concluded there was still uncertainty surrounding treatment duration and stopping rules*."

Table 3. EAG's deterministic base case results post technical engagement

Interventions	Total Costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)	ICER (£/QALY) - 1.2 severity weighting
BSC	[redacted]	[redacted]	-	-	-	-
Bulevirtide	[redacted]	[redacted]	[redacted]	[redacted]	£36,027	N/A - estimated severity weighting is 1.

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	ICER (£/QALY)	ICER (£/QALY) - 1.2 severity weighting
BSC	[redacted]	[redacted]	-	-	-	-
Bulevirtide	[redacted]	[redacted]	[redacted]	[redacted]	£36,950	N/A - estimated severity weighting is 1.

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 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.

Bulevirtide for treating chronic hepatitis D

PAS update

April 2023

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 133700.

1 Company updated results and EAG critique

In April 2023, the company updated the patient access scheme (PAS) discount for bulevirtide from [redacted] to [redacted]

The company's revised base case is provided in Table 1.

Table 1. Company's deterministic base case results in its third response after 2nd ACM (deterministic)

Interventions	Total Costs (£)	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)	ICER (£/QALY) - 1.2 severity weighting
BSC	[redacted]	[redacted]	-	-	-	-	-
Bulevirtide	[redacted]	[redacted]	[redacted]	4.39	[redacted]	£27,699	£23,083

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; inc, incremental; LYG, life years gained; QALY, quality adjusted life year

The EAG preferred base case is provided in Table 2.

Table 2. EAG preferred base case (deterministic)

Interventions	Total Costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)	ICER (£/QALY) - 1.2 severity weighting
BSC	[redacted]	[redacted]	-	-	-	-
Bulevirtide	[redacted]	[redacted]	[redacted]	[redacted]	£33,677	N/A – estimated severity weighting is 1

Abbreviations: BSC, best supportive care; EAG, external assessment group; ICER, incremental cost-effectiveness ratio; inc, incremental; N/A, not applicable; QALY, quality adjusted life year

Table 3 reports the results of Scenario B (Table 5) in the company's document entitled *Company Response to the EAG review (March 2023)*, as requested by NICE.

Table 3. EAG preferred base case (deterministic)

Interventions	Total Costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)	ICER (£/QALY) - 1.2 severity weighting
BSC	[redacted]	[redacted]	-	-	-	-
Bulevirtide	[redacted]	[redacted]	[redacted]	[redacted]	£29,824	£24,853

Abbreviations: BSC, best supportive care; EAG, external assessment group; ICER, incremental cost-effectiveness ratio; inc, incremental; N/A, not applicable; QALY, quality adjusted life year

Introduction

Following the second appraisal committee meeting (on 14 December 2022), the Company provided additional evidence (18 January 2023) discussing the Committee's preferred assumptions and high-level uncertainties. A total of 12 topics were discussed, with the Company revising the PAS discount downward from [redacted] per 30-vial pack of bulevirtide 2mg to [redacted] to mitigate any perceived residual decision uncertainty.

On 27 March 2023, the Company received the EAG's document (dated March 2023), which provides a brief review of the Company's January 2023 evidence. The EAG's review presented:

- a brief critique of 7 of the topics discussed in the Company's January evidence submission;
- a brief summary of the QALY shortfall calculation using the updated 'reference case' and model predicted median overall survival (OS); and
- the EAG's preferred assumptions and the resulting cost-effectiveness results.

This document outlines the Company's response to the EAG's March 2023 review document. The following topics are discussed:

1. Baseline fibrosis distribution based upon MYR 301.
2. Company's revised base-case model assumptions.
3. Company's revised cost-effectiveness results (deterministic and probabilistic).
4. Sensitivity and scenario analyses investigating the impact of the EAG's preferred assumptions on the Company's revised cost-effectiveness results.

Baseline fibrosis distribution based upon MYR 301

The patient cohort in the economic model starts by being distributed across one of three health states corresponding to METAVIR fibrosis stage F2, F3 and F4. The Committee expressed a preference for the baseline cirrhotic distribution in the economic model be based upon MYR 301. However, liver biopsy was not a requirement for inclusion in MYR 301 therefore a definitive assessment of METAVIR fibrosis stage at baseline is not available from MYR 301.

As previously noted by the EAG's clinical experts, liver biopsy is often not favoured by patients due to the invasive nature of the procedure and because is often deemed by clinicians as unnecessary in patients with evidence of advanced liver disease. Cirrhosis status of MYR 301 patients at screening (baseline) was determined according to clinical judgement of the investigators. As there is no universal definition of cirrhosis in HDV, investigators used a combination of clinical, histological (e.g., METAVIR, Ishak, and Knodell fibrosis scores) and other diagnostic measures (FibroScan) to confirm the presence or absence of cirrhosis.

In the economic model, it was therefore necessary to make a number of assumptions regarding the baseline cirrhotic distribution. Previously (January 2023), the Company assumed the proportion of patients with METAVIR fibrosis stage F4 in the economic model to be equal to the proportion of people in MYR 301 that had cirrhosis as assessed by clinical investigators at the time of enrolment, namely 47%[1]. The remaining non-cirrhotic patients (53%) were therefore assumed to occupy a single non-cirrhotic health state (achieved in the economic model by aggregating the F2 and F3 health states). Given the EAG did not approve of this approach, the Company has implemented an alternative approach using data from a post-hoc analysis of MYR 301.

Company's approach

Transient elastography (TE) is considered to be a reliable and well accepted method for diagnosing cirrhosis in patients with chronic liver diseases in UK clinical practice, however optimal cut-offs have not been fully established in HDV. A post-hoc analysis of patients' TE score, as assessed by FibroScan at enrolment in MYR 301, was undertaken in order to estimate the level of cirrhosis in patients at baseline, and in

[1] Liver biopsy was performed at baseline for [redacted] ([redacted] of 150 subjects) in MYR 301.

turn, calculate more accurate estimates of the distribution of patients across the health states in the economic model. Clinical advice received by the Company was that a FibroScan score of ≥ 12.5 kPA was an appropriate cut-off for METAVIR fibrosis stage F4. As stated in the EAG's recent review (27 March 2023), the EAG are of the opinion that a cut-off of [≥] 7.25 kPA is likely to align with METAVIR fibrosis stage F2. Table 1 presents the distribution of patients across different FibroScan cut-offs, and the resulting patient distribution across the fibrosis health states in the economic model.

Table 1: Baseline liver stiffness in MYR 301, full analysis set (Gilead Sciences, 2023)

Baseline liver stiffness (kPa)	Bulevirtide 2 mg (N=49)	Delayed treatment (N=51)	Both arms combined (N=100)	Proportion in equivalent fibrosis health state
< 7.25	[redacted]	[redacted]	[redacted]	N/A
≥ 7.25 to < 9.0	[redacted]	[redacted]	[redacted]	F2 = [redacted]
≥ 9.0 to < 12.5	[redacted]	[redacted]	[redacted]	F3 = [redacted]
≥ 12.5 to < 14.0	[redacted]	[redacted]	[redacted]	F4 = [redacted]
≥ 14.0	[redacted]	[redacted]	[redacted]	

Results from the post-hoc analysis (Table 1) show that the proportion of patients with cirrhosis as determined by FibroScan score (baseline liver stiffness ≥ 12.5 kPA) is consistent with the assessment of MYR 301 clinical investigators, namely that 47% of patients are cirrhotic.

The Company's revised base-case analysis uses the baseline FibroScan distribution from MYR 301 to distribute patients across equivalent health states in the economic model.

The Company's approach is considered to be more robust that the EAG's approach as it is based on evidence directly from the pivotal MYR 301 multi-centre randomised controlled phase III study investigating the safety and efficacy of bulevirtide compared to current best supportive care. In contrast, the EAG's approach is reliant upon a single study of patients who tested positive for HDV between 1978 and 2002 at a single hospital in Italy, namely Romeo *et al.,* (2009). It is acknowledged there is a paucity of data on fibrosis stating of CHD patients in the literature, however.

Company's revised base-case model assumptions

The Company has considered the EAG's (27 March 2023) preferred assumptions which has led to a revision to the Company's base-case; see Table 2.

Table 2: Comparison of EAG's preferred assumptions and the Company's revised base-case

Assumption	EAG preferred assumption	Company's (revised) base-case	Justification
1. Response rates from MYR 301	Full analysis set (FAS)	Same as EAG preferred assumption	• FAS maintains randomisation. • Whilst HDV patients in the UK are likely to be assessed using FibroScan, response rates in the FAS and in the FibroScan subgroup(s) are consistent. • Bulevirtide is more cost-effective when using response rates from the FibroScan subgroup(s), and response rates in the FibroScan subgroup(s) are marginally higher than those in the FAS, therefore assessing the cost-effectiveness of bulevirtide using the FAS is more conservative.
2. Baseline age from UKHSA (2022)	[redacted]	[redacted]	• The Committee requested to use the mean age from UKHSA (2022). • The Company's preferred data set is of HDV positive individuals who are alive (n=570), compared to the EAG's preferred data set which includes all HDV positive individuals (N=602), some of whom are deceased.
3. Probability of developing HCC	Assumption based on Alfaiate *et al.* (2020)	20%	• Clinical experts agreed that combined responders will still be at risk of HCC, therefore a low but not zero risk of progression to HCC for combined responders is assumed. • This is our understanding of the Committee's preferred assumption. • Note: an implementation error was corrected meaning that combined

			responders, irrespective of treatment, have the same probability of developing HCC.
4. Probability of fibrosis progression	Yes	Same as EAG preferred assumption	• Clinical experts agreed that combined responders will still be at risk of progression therefore a low but not zero risk of progression to HCC for combined responders is assumed. • This is our understanding of the Committee's preferred assumption. • Note: an implementation error was corrected meaning that combined responders (irrespective of treatment e.g., BLV or BSC) have the same probability of developing HCC.
5. Baseline fibrosis distribution	MYR 301 and Romeo *et al.* (2009)	MYR 301 post-hoc analysis	• Uses the MYR 301 clinical trial data. • Does not rely upon historic data of HDV patients in Italy. • Is more generalisable to the decision problem.
6. Natural history of fibrosis progression	Romeo *et at.* (2009)	As per original Company submission	• Based on systematic literature review and network meta-analysis. • Company applies a risk multiplier to reflect the increased risk of progression in CHD patients over CHB patients. • Approach validated with clinical experts at an advisory board. • Model predictions validated using published CHD literature (which the EAG agrees are reasonable). • EAG's approach has not been validated.
7. Natural history of HCC	Romeo *et al.* (2009) and Kushner *et al.* (2015)	As per original Company submission	

Company's revised cost-effectiveness results

Table 3 and Table 4 presents deterministic and probabilistic cost-effectiveness results as per the Company's revised base-case assumptions (as previously discussed in Table 2). Note, the results also incorporate changes to the QALY shortfall reference case and the QALY shortfall calculated produced by Schneider *et al.* (2021) which Schneider and the EAG have confirmed are correct.

Table 3: Deterministic cost-effectiveness results (March 2023)

Interventions	Total Costs	Total QALYs	Inc. Costs	Inc. QALYs	ICER (£/QALY)	
					Without severity modifier	With 1.2 severity modifier
Company base-case						
BSC	[redacted]	[redacted]	-	-	-	-
Bulevirtide	[redacted]	[redacted]	[redacted]	[redacted]	£29,629	£24,691

Note: the 1.2 severity modifier has been applied as the absolute QALY shortfall is [redacted] QALYs which is above the threshold of 12 QALYs for the 1.2 severity modifier.

Probabilistic sensitivity analysis (PSA) estimates the ICER associated with bulevirtide to be £25,117 per QALY gained, with the ICER below a £30,000 cost-effectiveness threshold 96% of the time.

Table 4: Probabilistic cost-effectiveness results (March 2023)

Interventions	Total Costs	Total QALYs	Inc. Costs	Inc. QALYs	ICER (£/QALY) With 1.2 severity modifier
Company base-case					
BSC	[redacted]	[redacted]	-	-	-
Bulevirtide	[redacted]	[redacted]	[redacted]	[redacted]	£25,117

Note: the 1.2 severity modifier has been applied as the absolute QALY shortfall is [redacted] QALYs which is above the threshold of 12 QALYs for the 1.2 severity modifier.

Sensitivity and scenario analyses

Ten sensitivity analysis were conducted to investigate the one-way and combined impact of the EAG's preferred assumptions on the Company's deterministic base-case cost-effectiveness results (see Table 5).

The Company's base-case analysis demonstrates that the QALY shortfall is sufficiently large (over 12 QALYs) that the 1.2 severity modifier should be applied. One-way sensitivity analysis demonstrates that bulevirtide qualifies for the 1.2 severity modifier when including/excluding each of the EAG's preferred assumptions. Furthermore, the QALY shortfall remains above 12 QALYs when in all but one of the EAG's preferred assumptions are implemented simultaneously, meaning the 1.2 severity modifier should be applied.

Table 5: Impact of the EAG's preferred assumptions on the Company's revised base-case cost-effectiveness results

EAG's preferred model assumptions	QALY shortfall	ICER	Difference vs. Company base-case
Company base-case	[redacted]	£24,691	-
1. Response rates from MYR 301	Already included in Company's base-case		
2. Baseline age from UKHSA	[redacted]	£24,782	£91
3. Probability of developing HCC	[redacted]	£26,677	£1,986
4. Probability of fibrosis progression	Already included in Company's base-case		
5. Baseline fibrosis distribution	[redacted]	£25,697	£1,006
6. Natural history of fibrosis progression	[redacted]	£25,454	£763
7. Natural history of HCC	[redacted]	£25,244	£553
Scenario A: all of the above except #5 (e.g., using the baseline fibrosis distribution from MYR 301 as per Company's base-case)	[redacted]	£27,908	£3,217
Scenario B: all of the above except #5 and #3	[redacted]	£26,599	£1,908
Scenario C: all of the EAG's preferred assumptions (#1 to #7)	[redacted]	£36,027 without severity modifier	£11,336
		£30,023 with severity modifier	£5,332

It is noteworthy, that whilst the EAG and the Company fundamentally do not agree on the most appropriate assumptions associated with the natural history of HDV (assumptions #6 and #7), the QALY shortfall is sufficiently large (over 12 QALYs) that the 1.2 severity modifier should be applied regardless of the natural history assumptions which are adopted by the Committee.

Scenario C is a highly pessimistic scenario which represents the most extreme set of assumptions offered for consideration by the EAG. Scenario C goes against the spirit of the Manual which specifically highlights that a higher degree of uncertainty is acceptable when considering rare disease and innovative technologies such as CHD and bulevirtide. Scenario C is therefore not a suitable estimate of the most likely ICER for bulevirtide. Only when the EAG assumes a significant proportion of the adult CHD population who have compensated liver disease and evidence of significant fibrosis, whose disease has responded inadequately to interferon-based therapy (or who are ineligible to receive interferon-based therapy due to intolerance or contraindication) have *less severe fibrosis*, does the QALY shortfall drop marginally below the threshold for the 1.2 severity modifier (as in Scenario C). This extremely conservative and methodologically contentious scenario highlights that the combined impact of the EAG's preferred assumptions results in 95.0% of the absolute QALY shortfall being achieved. In the most pessimistic scenario offered for consideration by the EAG (Scenario C), the ICER associated with bulevirtide is £30,023 per QALY gained when the 1.2 severity modifier is applied.

The Company has provided qualitative and quantitative evidence which supports the application of the severity modifier (see Company's January 2023 evidence). In addition, the Scottish Medicines Consortium (SMC) recently recognised the high unmet need and added value of bulevirtide, with bulevirtide fulfilling the PACE process criteria and being approved for use in NHS Scotland (SMC, 2023a; SMC 2023b).

The Company believes there is a high degree of certainty that the ICER for bulevirtide is sits between £24,691 per QALY gained (the Company's base-case) and £27,908 per QALY gained (Scenario A). Based on the totality of evidence, bulevirtide, a GB designated orphan drug with promising innovative medicines (PIM) designation, is expected to represent a cost-effective use of NHS resources and have a limited budget impact.

References

Alfaiate D, Clément S, Gomes D, Goossens N, Negro F. (2020) Chronic hepatitis D and hepatocellular carcinoma: A systematic review and meta-analysis of observational studies. J Hepatol. 2020 Sep;73(3):533-539. doi: 10.1016/j.jhep.2020.02.030.

Fattovich G. (2003) Natural history and prognosis of hepatitis B. Semin Liver Dis. Feb;23(1):47-58. doi: 10.1055/s-2003-37590.

Gilead Sciences Ltd. (2023) MYR 301 ad-hoc table: liver stiffness at baseline. Data on file.

Kushner T, Serper M, Kaplan DE. (2015) Delta hepatitis within the Veterans Affairs medical system in the United States: Prevalence, risk factors, and outcomes. J Hepatol. Sep;63(3):586-92. doi: 10.1016/j.jhep.2015.04.025.

Romeo R, Del Ninno E, Rumi M, Russo A, Sangiovanni A, de Franchis R, Ronchi G, Colombo M. (2009) A 28-year study of the course of hepatitis Delta infection: a risk factor for cirrhosis and hepatocellular carcinoma. *Gastroenterology*. May;136(5):1629-38. doi: 10.1053/j.gastro.2009.01.052.

Schneider, P., McNamara, S., Love-Koh, J., Doran, T., and Gutacker, N. (2021) QALY Shortfall Calculator. Available online: https://r4scharr.shinyapps.io/shortfall/ [Accessed 08 March 2023].

Scottish Medicines Consortium (SMC) (2023a), PACE statement for bulevirtide [SMC2520]. 17 Jan 2023.

Scottish Medicines Consortium (SMC) (2023b), bulevirtide 2mg powder for solution for injection (Hepcludex®) Advice: SMC2520. 10 Feb 2023.

UK Health Security Agency (UKHSA) (2022). Mean age of HDV RNA positive patients at baseline. Data on File.

Bulevirtide for treating chronic hepatitis D

Review of the company's second response

March 2023

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 EAG's review of the company's second response following from the second appraisal committee meeting (ACM).

2 Company updated results and EAG critique

In January 2023, the company updated the patient access scheme (PAS) discount for bulevirtide from [redacted] to [redacted], which remains unchanged. In March, the company submitted a document with two additional issues for consideration:

1. The long-term survival and disease severity related to chronic hepatitis D (CHD).
2. The use of the severity modifier of 1.2 in the base case analysis.

The company did not change the assumptions in the model previously submitted in January, therefore the company's base case ICER also did not change (Table 1).

In Table 2, the EAG summarises the EAG critique of the company's response, which includes all the issues for consideration since the second ACM in January up to now.

Table 1. Company's deterministic base case results post second ACM

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]	£29,083	£24,236

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. Changes in company's model post second ACM

Assumption in company's model submitted in March 2023	EAG critique	Committee's preference at second ACM?	Included in EAG's preferred assumptions?
1. The response rates in the model reflect those of the subgroup of patients from MYR301 with a FibroScan® score greater than or equal to 8 kPa.	FibroScan® is not very accurate in diagnosing significant fibrosis (equivalent of METAVIR ≥F2); however, it is likely what will be used to identify patients eligible for bulevirtide in clinical practice. Of the two cut-offs put forward by the company, 8.0 kPa is likely to align more with METAVIR F3 and a cut-off of 7.25 kPa is likely to be closer to METAVIR F2. However, response data from MYR 301 using either of these cut-offs are similar to the results of the full trial population. As the inclusion of patients without significant fibrosis (METAVIR F0 or F1) has limited impact on the efficacy, the EAG prefers to use the full trial population which is more methodologically robust than the *post hoc* subgroup that breaks randomisation.	No (committee preference is for METAVIR stage ≥F2 to align with CG165)	The EAG preferred assumption remains to use the response data for the full trial population over either of the suggested subgroups.
2. The baseline age in the model is [redacted] years as per the UKHSA study.	The EAG disagrees with the company's implementation of this assumption in the model as the company assumed the baseline age to be [redacted].	Yes (however not specified if preference was [redacted] or [redacted] years)	Yes, however the EAG preference is to use the mean age reported for the full dataset available in the UKHSA study (37.4 years).
3. Assumed that CRs had a probability of developing HCC, estimated as 20% of that assumed for PRs.	The EAG notes the same implementation error (as that identified in January 2023) in the model whereby bulevirtide CRs have 20% of the probability of bulevirtide PRs of developing HCC, while BSC CRs have the same probability (instead of 20%) as BSC PRs of developing HCC. The EAG corrected this in the model and provides the results for the company's corrected base case in Table 3.	Unclear. The committee agreed with the clinical experts that CRs would still be at risk of HCC. The committee noted that the EAG assumed a residual risk of HCC in its base case and preferred	No. The EAG preferred assumption remains that of assuming that CRs and PRs have the same probability of developing HCC. This is a conservative assumption based on the Alfaiate study suggesting that HCC is likely to occur even in patients considered to be complete responders (as discussed in the EAG original report).

	The assumption included in the EAG's original base case was that CRs and PRs have the same probability of developing HCC.	to align with the EAG's assumption on this.	Nonetheless, the EAG reports results for its preferred ICER when the company's assumption is used in Section 3.
4. Assumed that CRs had a probability of experiencing fibrosis progression, estimated as 20% of that assumed for PRs.	The EAG notes the same implementation error (as that identified in January 2023) in the model where bulevirtide CRs have 20% of the probability of bulevirtide PRs of having fibrosis progression while BSC CRs have a 0% probability of progressing. The EAG corrected this in the model and provides the results for the company's corrected base case in Table 3.	Yes. Clinical experts at committee noted that CRs could still experience a low risk of progression through fibrosis stages.	Yes. Given the committee's conclusion that CRs can still experience fibrosis progression the EAG corrected the implementation of this scenario in the model and included it in its preferred assumptions.
5. Assuming that the baseline proportion of patients with METAVIR fibrosis stage F4 is 47% at baseline (based on MYR301) and aggregating the baseline proportion of patients in the F2 and F3 states (53% of patients) to occupy the F3 health state at baseline.	The EAG-preferred assumption (as discussed in the EAG original report) is to use the 47% estimate from MYR301 for the F4 state and to assume that 22% and 31% of patients were in the F2 and F3 states at baseline, respectively, instead of assuming that 53% of patients are in the F3 state at baseline. The MYR301 study only reported the baseline distribution of patients in the F4 state (47%) or below (53%) but did not provide the baseline split between patients in the F2 and F3 states. Given that there is no evidence to suggest that patients in MyR301 were only in the F4 or F3 states, the EAG used the Romeo *et at.* distribution at baseline, re-weighted by the 53% of patients in the F2 and F3 states at baseline in MYR301. Assuming that patients all 53% of patients are in the worse state (F3) at baseline (instead of distributed between the F3 and F2 states) leads to an incremental advantage for bulevirtide in the model as patients in the F3 state have a higher probability of	The committee agreed with the use of the MYR301 baseline distribution of fibrosis.	No. The EAG assumed that 22% and 31% of patients were in the F2 and F3 states at baseline, respectively.

	HCC, and also progress faster to the F4 state, where the probability of HCC is even higher.		
6. In order to estimate the natural history of fibrosis progression in the model, the company used a study reporting the cumulative incidence of cirrhosis in people with chronic hepatitis B (CHB) and then applied a multiplier from another study to reflect the increase in risk of cirrhosis for patients with CHB co-infected with CHD.[1,2]	As discussed in Section 4.2.5.3.1 of the EAG's original report, the EAG's preference to estimate the natural history of fibrosis progression (i.e., for non-responders) is to directly use the probability of fibrosis progression from the F2-F4 states for patients with CHD according to the Romeo et al. 2009 study. The study reported estimates of progression from the different METAVIR stages to the compensated cirrhosis stage for HDV positive patients.[3] (Table 26 the EAG original report).	Not specifically stated.	No.
7. In order to estimate the natural history of HCC in the model, the company used several studies for the probability of HCC in patients with CHB and then estimated the increase in risk of HCC for patients with CHB co-infected with CHD.[4,5,6,7]	As discussed in Section 4.2.5.3.1 of the EAG's original report, the EAG's preference is to estimate the probability of HCC for non-responders directly from a source which includes CHD patients. Therefore, the EAG preference remains to estimate the probability of HCC from the F2-F4 states according to Romeo and Kushner (Table 25 of the EAG original report).[3,8]	Not specifically stated.	No.
Abbreviations: BSC, best supportive care; EAG, evidence assessment group; ICER, incremental cost-effectiveness ratio; HCC, hepatocellular carcinoma; CR, complete responders; PR, partial responders			

Table 3. Company's deterministic base case results post second ACM – corrected by the EAG

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]	£29,031	£24,192

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

Furthermore, the company reported that its base case model predicts a median survival of 45.2 years for people receiving BSC and 52.8 years for people treated with bulevirtide (Figure 1 in company's response). However, the EAG is unsure how the company obtained the survival trace provided, as the company's base case model results in a survival trace reported in Figure 1 below. Baseline age in the model is 37 years, which suggests that median survival in the company's base case model is approximately 56 years for BSC patients and 73 years for bulevirtide patients (median OS gain of 17 years).

The company adds that the median age of death in the matched general population is estimated to be 83 years of age (Schneider *et al.* 2021), which would imply a 27- years of life lost for patients in BSC. The company argues that there is a substantial reduction in median OS, thus demonstrating that CHD is a severe disease.

The EAG notes that the use of a disease severity modifier is not based on median survival times, but instead on the mean total QALY loss associated with being untreated for a specific disease over a patients' lifetime.

As outlined in the NICE methods guide,[9] "*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 4.

The QALY shortfall should be estimated using the published calculator by Schneider *et al*. 2021.[10] The tool calculates the expected total QALYs for the general population matched to baseline age and sex distribution included in the economic model. The company noted that since January, the preferred

HRQoL norms and assumptions in Schneider *et al.* 2021 have been updated. In light of this updated, the company reported that the absolute QALY shortfall in the model should be:

- 13.08 QALYs using the company's preferred assumptions;
- 12.15 QALYs using the EAG's preferred assumptions.

Whereas the EAG agrees that in the company's base case the total BSC QALY estimation leads to an absolute QALY shortfall estimate of 13.08 (or 13.06 in the EAG-corrected base case) in the updated Schneider *et al*. 2021 calculator (therefore meaning that a 1.2 severity weight should be used), the same is not the case for the EAG-preferred base case.

The company reports that the EAG-preferred base case without a severity modifier is £31,119; however, the EAG is unclear how the company reached this estimate. The EAG-preferred ICER is £36,027 (as previously reported in the EAG's response to the company's comments in January and as discussed in Section 3). The EAG-preferred assumptions in the model lead to an absolute QALY shortfall estimate of 11.40 in the updated Schneider *et al*. 2021 algorithm (therefore meaning that a 1 severity weight should be used).

Figure 1. Overall survival in the model

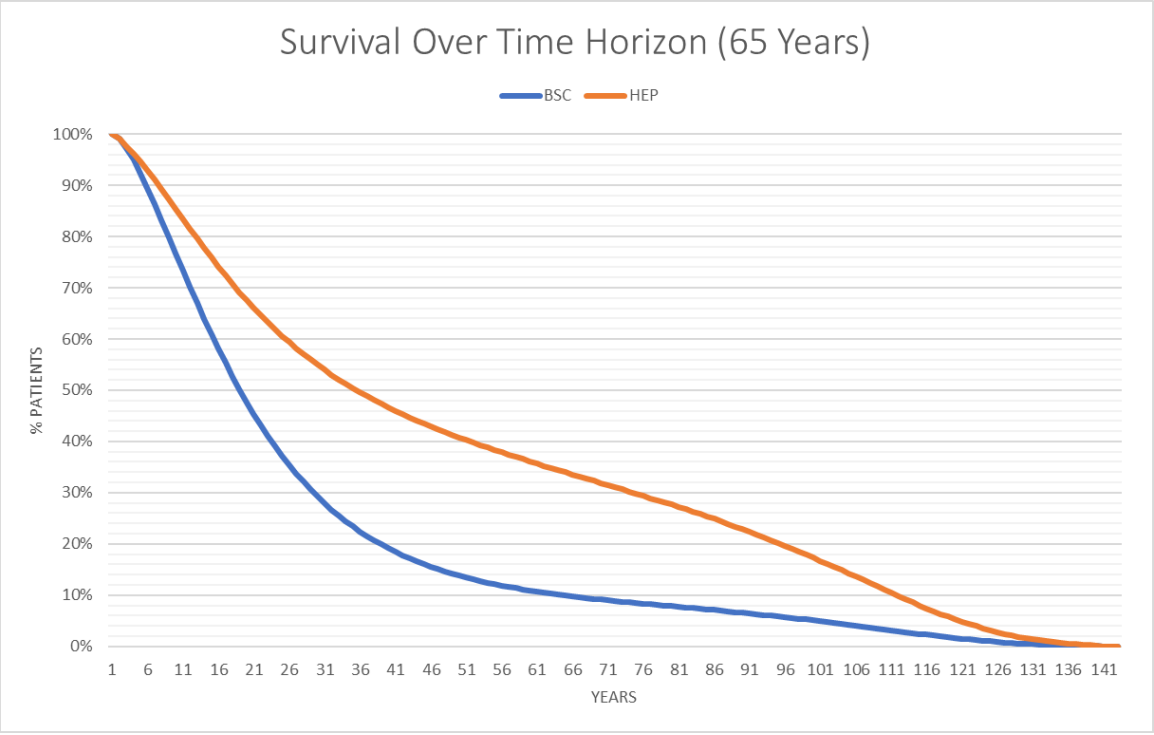


Table 4. QALY weighting for severity

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

3 EAG preferred assumptions

Table 5 reports the EAG's deterministic ICERs, including all EAG's preferred assumptions differing from those used by the company (as detailed in Table 1). These consist of the following:

- Using the response data for the full MYR 301 trial population.
- Using the mean age reported in the UKHSA study ([redacted] years).
- Using the cirrhotic distribution at baseline to reflect the MYR 301 population (47% of patients with compensated cirrhosis and 22% and 31% of patients in the F2 and F3 states at baseline, respectively).
- Estimation of the probability of HCC for non-responders from the F2-F4 states according to Romeo[3] and Kushner.[8]
- Estimation of the probability of fibrosis progression for non-responders from the F2-F4 states according to Romeo.[3]
- Assuming that CRs have the same probability as PRs (which is lower than the probability of non-responders) of developing HCC.

These changes are included in the ICER reported in Table 5 and Table 6, for the deterministic, and probabilistic ICERs.

The EAG-preferred deterministic ICER amounts to £36,027. The EAG notes that the economic results are not eligible for the use of a severity weighting given that with a baseline age of 37 years and a female distribution of 41%, the total QALYs associated with BSC would have to be 7.37 (or below) in order for the severity weighting to be 1.2. The EAG notes that this contrasts with the 6.6 QALYs needed in the outdated Schneider *et al*. 2021 calculator. Given that the EAG-preferred base case ICER generates a total QALY gain of [redacted] for BSC, the difference to the calculator threshold (of 7.37) at which the 1.2 weight would be applicable, still differs by [redacted] QALYs.

The EAG also notes that when the company's less conservative assumption is used in the model, whereby CRs have a lower probability of developing HCC than PRs (see issue 3 in Table 2), the EAG-preferred ICER amounts to £34,381, and the total QALYs for the BSC arm are [redacted] (thus making the ICER not applicable for a QALY weighting of 1.2).

Finally, the EAG notes that all the ICERs herein provided remain highly uncertain with regards to the duration of treatment response and duration of treatment in the economic model. 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 then discontinue treatment (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.

Crucially, the EAG notes that the 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. At the second ACM, the committee, "*recognised there remained some ambiguity in how long treatment should continue treatment and when people who do not respond to treatment should stop having bulevirtide*[…] *The committee concluded there was still uncertainty surrounding treatment duration and stopping rules*."

Table 5. EAG's preferred model assumptions - deterministic

Preferred assumption	Total QALYs for BSC	Cumulative ICER (£/QALY)	Cumulative ICER (£/QALY) - 1.2 severity weighting
Company revised base case post technical engagement (corrected)	[redacted]	£29,031	£24,192
Using the response data for the full trial population	[redacted]	£28,787	£23,989
Using the mean age reported in the UKHSA study	[redacted]	£28,891	£24,076

Cirrhotic distribution at baseline reflects the MYR 301 population (47% of patients with compensated cirrhosis)	[redacted]	£30,954	£25,795
Estimation of the probability of HCC from the F2-F4 states according to Romeo[3] and Kushner[8]	[redacted]	£31,920	£26,600
Estimation of the probability of fibrosis progression from the F2-F4 states according to Romeo	[redacted]	£34,381	N/A - estimated severity weighting using is 1.
Assuming that CRs have the same probability as PRs (which is lower than the probability of non-responders) of developing HCC.	[redacted]	£36,027	N/A - estimated severity weighting using 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 6. EAG's probabilistic base case results

Interventions	Total Costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)	ICER (£/QALY) - 1.2 severity weighting
BSC	[redacted]	[redacted]				-
Bulevirtide	[redacted]	[redacted]	[redacted]	[redacted]	£36,704	N/A - estimated severity weighting is 1.

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 References

1. 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, 2003:47-58.
2. Da BL, Heller T, Koh C. Hepatitis D infection: From initial discovery to current investigational therapies. *Gastroenterology Report* 2019;7(4):231-45. doi: 10.1093/gastro/goz023
3. 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
4. Hsu YS, Chien RN, Yeh CT, et al. Long-term outcome after spontaneous HBeAg seroconversion in patients with chronic hepatitis B. *Hepatology* 2002;35(6):1522-27. doi: 10.1053/jhep.2002.33638
5. Dienstag JL, Ghany MG, Morgan TR, et al. A prospective study of the rate of progression in compensated, histologically advanced chronic hepatitis C. *Hepatology* 2011;54(2):396-405. doi: 10.1002/hep.24370
6. Bermingham SL, Hughes R, Fenu E, 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(6):800-09. doi: 10.1016/j.jval.2015.05.007
7. Alfaiate D, Clément S, Gomes D, et al. Chronic hepatitis D and hepatocellular carcinoma: A systematic review and meta-analysis of observational studies. *Journal of Hepatology* 2020;73(3):533-39. doi: https://doi.org/10.1016/j.jhep.2020.02.030
8. 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.
9. NICE. NICE health technology evaluations: the manual, 2022.
10. Schneider P, McNamara S, Love-Koh J, et al. Quality-adjusted life expectancy norms for the English population, 2021.