

Medical Services Advisory Committee (MSAC) Public Summary Document

Application No. 1708.1 - Hepatitis delta virus (HDV) RNA PCR testing to determine eligibility for PBS-subsidised bulevirtide (HEPCLUDEX) for treatment of HDV

Applicant: Gilead Sciences Pty Ltd

Date of MSAC consideration: 3-4 April 2025

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](#)

1. Purpose of the application

The integrated codependent application requested:

- Medicare Benefits Schedule (MBS) listing of testing for serum or plasma hepatitis D virus (HDV) ribonucleic acid (RNA) by polymerase chain reaction (PCR) for the determination of patient eligibility for treatment with bulevirtide in patients with chronic hepatitis D (CHD); and
- Pharmaceutical Benefits Scheme (PBS) Section 100, Authority Required – Streamlined listing of bulevirtide for the treatment of CHD in patients with compensated liver disease and detectable HDV RNA.
- MSAC has previously considered HDV RNA PCR testing for access to bulevirtide for the treatment of CHD. The original submission was considered by MSAC at its April 2024 meeting.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC supported the creation of a new Medicare Benefits Schedule (MBS) item for the quantitation of Hepatitis D viral (HDV) ribonucleic acid (RNA) using polymerase chain reaction (PCR) testing to i) determine eligibility for treatment with bulevirtide and ii) monitor the efficacy of bulevirtide treatment in patients with chronic HDV infection with compensated liver disease. MSAC noted that the Pharmaceutical Benefits Advisory Committee (PBAC) at its March 2025 meeting was of a mind to recommend the Pharmaceutical Benefit Schedule (PBS) listing of bulevirtide, pending MSAC's advice on the test. The PBAC considered that bulevirtide would be cost-effective with a further substantial price reduction, to reflect the remaining uncertainties in the economic model.

MSAC considered that HDV RNA testing is necessary to determine eligibility for bulevirtide treatment because the test is needed to confirm whether a patient has an active HDV infection. MSAC considered that the evidence for monitoring HDV RNA levels during bulevirtide treatment was limited. However, MSAC considered that reduction in HDV RNA levels may reflect response to bulevirtide treatment. MSAC considered viral load quantification on bulevirtide treatment would be consistent with the management of other chronic viral hepatitis infections where virus load quantification is the standard of care. MSAC considered that there is a high clinical need for treatments for chronic HDV infection as it is a rare and aggressive condition with limited treatment options that is more common in socially vulnerable groups.

MSAC noted that while some uncertainty remained around the number of HDV RNA tests likely to be required and hence the resulting MBS financial impact, the financial impacts of testing were modest in absolute terms and in comparison to the costs of the treatment. MSAC supported a single new MBS item to determine eligibility and monitoring that could be requested by, or on behalf of, a specialist or consultant physician. MSAC considered that the item descriptor should allow the test to be used to determine eligibility for future Pharmaceutical Benefit Schedule (PBS) listed treatments for this patient group and supported a fee of \$152.10.

Category 6 – PATHOLOGY SERVICES

Group P3 - Microbiology

MBS item *XXXX

Quantitation of Hepatitis D viral RNA load in plasma or serum, requested by a specialist or consultant physician, or a general practitioner in consultation with a specialist or consultant physician, for:

- a) a patient who is Hepatitis D viral antibody positive and suspected of having chronic hepatitis D, to determine eligibility for a treatment listed on the Pharmaceutical Benefits Scheme (PBS); or
- b) a patient undertaking anti-viral therapy for chronic hepatitis D with a PBS listed treatment, for the purpose of assessing treatment effectiveness.

To a maximum of 2 tests in a 12 month period

Fee: \$152.10 Benefit: 75% \$114.10 85% = \$129.30

Consumer summary

This is an application from Gilead Sciences requesting Medicare Benefits Schedule (MBS) listing of a test to detect the hepatitis D virus in patients. The test results would be used to diagnose active hepatitis D infection and so provide access to a treatment called bulevirtide, and to monitor how well bulevirtide was helping the patient fight hepatitis D. This was a co-dependent application, with MSAC considering the testing and the Pharmaceutical Benefits Advisory Committee (PBAC) considering the medicine (bulevirtide). MSAC and the PBAC had previously considered this application in April 2024, but did not support listing, so this was a resubmission of the application. The PBAC had considered the resubmission at its March 2025 meeting and deferred its decision on PBS listing of bulevirtide, but was of a mind to support it, if MSAC supported the test. The PBAC also considered that bulevirtide would be good value for money if its price was further reduced.

Hepatitis D is an infection of the liver. It can result in cirrhosis (scarring) and liver cancer. Some people may develop end-stage liver disease and liver failure. There is currently no treatment available specifically for hepatitis D.

The hepatitis D virus only infects people who are already infected with the hepatitis B virus. Hepatitis B and D are relatively rare in Australia because there is an effective hepatitis B vaccine available. However, hepatitis B and D are more common in people born overseas, people from culturally and linguistically diverse communities, people who inject drugs, and men who have sex with men.

The test is also known as a HDV RNA PCR test. HDV refers to the hepatitis D virus and RNA refers to ribonucleic acid, which is a genetic material found in all living cells. PCR refers to polymerase chain reaction, which is a testing method used to rapidly make copies of genetic material and amplify it to a large enough amount to study in detail. The test can identify whether someone has a hepatitis D infection and can also measure the amount of virus present in the infected person's liver. The test works by measuring how much genetic material (RNA) from the hepatitis D virus there is in a blood sample from the patient, using the PCR testing method.

Bulevirtide is a medication that works by preventing the hepatitis D virus from entering liver (hepatic) cells. This application proposed testing people who may have chronic hepatitis D, and if they test positive, they can start bulevirtide treatment. Once on treatment, they would continue to have their levels of HDV RNA monitored to see how well the treatment is working.

MSAC noted that there was no new evidence available, but the applicant had addressed MSAC's concerns from the previous submission. In particular MSAC considered that the applicant had demonstrated the clinical need for the test to monitor by quantitative measurement of a patient's levels of HDV RNA how well bulevirtide was helping the patient fight hepatitis D.

MSAC's advice to the Commonwealth Minister for Health and Aged Care

MSAC supported MBS listing of HDV RNA PCR testing to determine eligibility for treatment with bulevirtide and to monitor the response to treatment. MSAC considered that the test was safe and effective, and that the test and treatment would provide good value for money in these patients.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted that this application from Gilead Sciences was for Medicare Benefits Schedule (MBS) listing of ribonucleic acid (RNA) polymerase chain reaction (PCR) testing to detect hepatitis delta virus (HDV) RNA to determine eligibility for treatment with bulevirtide in patients with chronic HDV with compensated liver disease, and to quantify the levels of HDV RNA for monitoring the efficacy of bulevirtide treatment. This was a co-dependent application with the Pharmaceutical Benefits Advisory Committee (PBAC), MSAC and the PBAC had previously considered this application in April 2024 and did not support listing at the time. MSAC had considered that there was insufficient clinical justification for the RNA test since the PBAC did not support listing of bulevirtide, and the case for codependency between testing and bulevirtide use was not sufficiently established (see the [public summary document](#) on the webpage for application 1708 on the MSAC website). MSAC noted that the PBAC had deferred its decision on the resubmission in its March 2025 meeting, but was of a mind to support the application pending MSAC's advice on the test. The PBAC considered that bulevirtide would be cost-effective with a further substantial price reduction, to reflect the remaining uncertainties in the economic model and bring the ICER into an acceptable range.

MSAC noted that there is an unmet clinical need, in terms of a need for the detection and treatment of patients with chronic hepatitis D virus (HDV) infection. MSAC noted that HDV infections occur within a setting of an infection with chronic hepatitis B virus (HBV) and are associated with a more aggressive disease course compared with HBV mono-infection including an increased risk of development of acute hepatic failure, cirrhosis, hepatic decompensation and hepatocellular carcinoma. The 5-year mortality from superinfection of HDV in patients with HBV is twice that of HBV mono-infection. MSAC noted that HDV infection is likely significantly higher in people born overseas, people from culturally and linguistically diverse (CALD) backgrounds, intravenous drug users, and men who have sex with men (MSM), all of whom may experience barriers to healthcare access. MSAC noted there is currently no approved treatment for HDV in Australia.

MSAC noted that the proposed test uses commercial or in-house reverse transcriptase polymerase chain reaction (PCR) assays. MSAC noted that while a decrease of 2 log₁₀ IU/ mL in the HDV RNA level from the original viremic titre is used in trials as a surrogate marker of potential benefit from treatment with bulevirtide, this ultimately requires confirmation with improvements in clinical end points such as progression to cirrhosis, hepatocellular carcinoma (HCC), and death. MSAC noted that that no threshold for a serum HDV RNA level (other than undetectable HDV RNA) corresponding to a clinical benefit has yet been defined. MSAC recalled that the test used in the key clinical trial (MYR301) was Robogene HDV RNA PCR, with a lower limit of detection (LLOD) of 6 IU/mL. MSAC noted that although the commercially available Victorian Infectious Diseases Reference Laboratory (VIDRL) test **redacted**. MSAC noted that in the key trial, compared to patients in the control group, the treatment group had a significantly higher proportion of patients with undetectable or at least a 2 log₁₀ decrease in HDV RNA and normalisation of alanine transaminase (ALT). However, MSAC considered that longer-term data would be needed to demonstrate clinical benefit.

MSAC noted no claims were made about the safety of HDV RNA PCR testing in the previous submission or in the resubmission. While the commentary raised the risks of false negative results due to the use of suboptimal assays and/or a higher LLOD associated with in-house assays in current use, MSAC considered that it was unknown whether this would result in a clinically important difference. MSAC noted that there is no accreditation or external quality assurance program (QAP) for HDV RNA testing in Australia. In addition, currently there is only one laboratory in Australia that conducts this testing, MSAC noted that this is unlikely to be a significant issue as uncommon tests frequently do not have their own QAP. The applicant advised that it would support an external QAP in the future if other laboratories decided to offer HDV testing.

On the clinical effectiveness of the test, MSAC recalled that the presence of HDV RNA on PCR testing was inconsistently associated with poorer health outcomes (three out of five studies reported statistically significant associations). MSAC recalled that the evidence for the prognostic benefit of testing using the baseline presence or absence of HDV RNA was severely confounded by treatment variability across studies, and therefore the evidence was at a high risk of bias. MSAC noted that this resubmission did not include significant new evidence or data to reduce the uncertainty of the previously assessed evidence, as no new information was available (as noted in the applicant's pre-MSAC response). MSAC accepted that the evidence is limited as HDV is relatively rare and would require a prolonged follow-up time and the best available evidence has been considered. It is unlikely that there will be further on-treatment data available.

MSAC recalled that it had previously specified that any resubmission should consider whether there was merit in proposing qualitative rather than quantitative testing, given the lack of evidence that the levels of HDV RNA inform decision making and the lack of a clear consensus on the threshold reduction in viral load that would inform changes in clinical management. MSAC agreed with ESC that the claim that a reduction in quantitative HDV viral load levels relative to baseline was indicative of clinical response to treatment was biologically plausible insofar as patients with lower detectable viral loads may have a reduced risk of developing liver-related clinical events (e.g. cirrhosis, hepatocellular carcinoma) compared to patients with higher detectable viral loads. MSAC also noted and considered reasonable the applicant's response that quantitative testing of viral load is the standard of care for patients with chronic viral hepatitis, including Hepatitis B and C. The Department had also received information from the Victorian Infectious Diseases Reference Laboratory (VIDRL) that there is no appropriate qualitative test currently available for Hepatitis D. MSAC therefore concluded that quantitative testing was appropriate.

MSAC had requested that the applicant identify continuation and discontinuation criteria for bulevirtide, to provide more certainty around the likely duration of treatment and the number of tests required for monitoring treatment. MSAC noted the applicant in the pre-MSAC response, had considered that this should be left to clinical judgement based on response to treatment and PBAC had not recommended continuation criteria based on ongoing testing. However, MSAC considered that, given the benefits of the treatment may be driven by a reduction in viral load that can be measured with the quantitative test, the PBAC may wish to consider including continuation or discontinuation criteria for bulevirtide. A decrease of 2 log₁₀ international units (IU)/mL in the HDV RNA level from the original viremic titre indicates potential benefit. The applicant's pre-MSAC response noted that the United States Food and Drug Administration had also adopted this threshold in its guidance for chronic HDV trial outcomes.

MSAC noted that the economic evaluation in the resubmission included the cost for 6 monthly HDV RNA testing but the only change in management that was modelled was to cease treatment in non-responders at week 144. MSAC recalled that it had requested that the applicant provide additional clarity around the likely pattern of testing and re-testing to better inform the economic evaluation. This had not been adequately addressed in the resubmission. However, MSAC considered that testing should be limited to twice per year, which is in line with viral load testing for hepatitis B, and would also be expected to be in line with patient preferences for testing frequency. MSAC noted that the high ICER from the economic evaluation is still a concern although the resubmission already included a reduction in the price of bulevirtide. MSAC also noted PBAC's consideration (as discussed above) that bulevirtide would be cost-effective with a further reduction in its price.

MSAC noted that the cost of the codependent submission is predominantly due to the treatment and not the testing, which has a very modest financial impact. The total net cost to the Commonwealth over the first 6 years of MBS and PBS listings was \$100 million to < \$200 million of which only approximately \$0 to < \$10 million was the cost of testing to the MBS. MSAC noted ESC's advice that there is some uncertainty regarding the utilisation estimates presented in the ADAR regarding discontinuation of treatment but also considered that there was unlikely to be better data available to inform this.

Overall, MSAC considered that its concerns from the previous submission had been addressed as much as possible, and supported MBS listing of HDV RNA testing alongside PBS listing of bulevirtide. MSAC confirmed that a single new MBS item should be created for the purpose of determining eligibility for treatment as well as for monitoring. MSAC also noted the PBAC's request for MSAC to consider allowing general practitioners (GPs) to order the test, given that access to specialists is likely to be difficult for many patients with hepatitis D. These access issues were also highlighted in consultation inputs from several hepatitis organisations. MSAC considered that GPs would not be likely to order this test routinely without consulting with a specialist and given the small cohort of patients there would be unlikely to be issues with inappropriate ordering of the test and therefore there would not be a strong case for restricting ordering to specialists. Thus MSAC confirmed that the MBS descriptor should specify that the test can be ordered 'by a specialist or consultant physician, or a GP in consultation with a specialist or consultant physician'. MSAC noted the Department's advice that access to fibroscan/transient elastography is not MBS funded but is not a requirement for access to bulevirtide. MSAC also confirmed that the item descriptor should be treatment agnostic to allow it to be used to determine eligibility for future PBS-listed treatments for this patient group. MSAC confirmed that the fee of \$152.10 was appropriate.

4. Background

MSAC Application 1708 was considered by MSAC at a meeting on 4-5 April 2024. The Public Summary Document (PSD) summarised the meeting outcomes on page 8. MSAC was not supportive of the application and identified several deficiencies. These issues and any additional issues raised in the MSAC PSD, for Application number 1708 are outlined in Table 1. The response in the resubmission and the adequacy of this response as assessed by the commentary are also summarised in Table 1. Key components of the clinical issue addressed by the resubmission are summarised in Table 2.

Table 1 MSAC concerns and how these were addressed in the resubmission

MSAC issue to be addressed	How it is addressed in the resubmission	Was the issue addressed adequately? (as assessed by the commentary)
MSAC considered that a resubmission would need to: (page 8-9 of the PSD)		
Consider whether there was merit in proposing qualitative rather than quantitative testing for treatment eligibility and monitoring, given the lack of evidence that the levels of HDV RNA inform decision making. (paragraph 3, page 5 of the PSD)	<p>Gilead are not aware of a qualitative test for HDV RNA available in Australia and have confirmed with VIDRL that they do not have, nor are aware of, a qualitative HDV RNA test. Therefore, any qualitative assessment of HDV RNA requires the HDV RNA PCR test proposed for MBS listing in this resubmission to be conducted to determine presence of (qualitative) HDV RNA which can also derive a HDV RNA viral load (quantitative).</p> <p>In order to determine the clinical benefit of HEPCLUDEX, change in HDV RNA viral load is required which means a quantitative assessment is necessary at baseline (i.e., prior to initiating treatment), and when continuing on treatment. If clinical benefit is observed (i.e., a reduction in</p>	<p><i>Qualitative assessment of HDV RNA requires the reporting of HDV RNA being detectable vs undetectable. The commentary considered that this would likely be sufficient for determining eligibility for, or cessation of treatment with bulevirtide. The qualitative concordance between different tests is high.</i></p> <p><i>The commentary considered that qualitative assessment of HDV RNA would also be sufficient for monitoring treatment if the endpoint was sustained undetectable HDV RNA. It also has prognostic value.</i></p> <p><i>However refer to 'Summary of consideration and rationale for MSAC's advice'.</i></p>

MSAC issue to be addressed	How it is addressed in the resubmission	Was the issue addressed adequately? (as assessed by the commentary)
	<p>HDV RNA viral load from baseline), a decision is made to continue patients on HEPCLUDEX treatment.</p> <p>Conversely, if no clinical benefit (i.e., no reduction in HDV RNA viral load from baseline) is observed for patients treated with HEPCLUDEX, a decision is made to stop treatment.</p>	
<p>In the key clinical trial, MYR301, a decrease of $2\log_{10}$ international units [IU]/mL in the HDV RNA level from the original viremic titre was used as a surrogate marker of potential benefit. However, evidence was required that a decrease in HDV RNA levels of at least this magnitude correlated with improvements in clinical end points such as progression to cirrhosis, HCC and death. MSAC considered this important, and this was not confirmed in the key trial. MSAC also noted that a threshold had not yet been defined for a serum HDV RNA level (other than undetectable HDV RNA) that corresponded to a clinical benefit. (paragraph 5, page 5 of the PSD)]</p>	<p>HEPCLUDEX is proposed for ongoing use as long as associated with clinical benefit which, as stated by the PBAC, considers the “decision to continue or cease treatment, based on response, [i]s a matter of clinical judgement” [RATIFIED] 5.06 bulevirtide MINS 03-2024 Item 7.46 P 46, Attachment 01].</p>	<p><i>The commentary considered that to date, there is little evidence to support a decline of $>2\log_{10}$ IU/mL as having a prognostic effect. However, there is some evidence to suggest that an early decrease in HDV RNA from baseline is predictive of treatment response. In this case quantitative HDV RNA values would be required to determine early virological decreases or non-response to treatment.</i></p> <p><i>If a decrease of $>2 \log_{10}$ IU/mL is considered an accepted treatment endpoint, quantitative values would be required to determine this.</i></p> <p><i>Note: the concordance between tests for quantitative measurement of HDV RNA has several reliability issues.</i></p>
<p>Identify continuation and discontinuation criteria, to provide more certainty around the likely duration of treatment and the number of tests required for monitoring treatment.</p> <p>[MSAC considered that there were no continuation or discontinuation criteria for treatment outlined in the application or included in the clinical management algorithm. As a result, there was uncertainty in the duration of treatment and the number of monitoring tests required per treated patient. MSAC disagreed with the pre-MSAC response, which stated that continuation and discontinuation criteria were unnecessary. (paragraph 7, page 5 of the PSD)]</p>	<p>This is aligned with the TGA-registered HEPCLUDEX product information (PI) which states clinically “treatment should be continued as long as associated with clinical benefit” and consistent with the restrictions for the treatment of patients with CHB on the PBS (who are managed by the same prescriber).</p> <p>Similar to other viral hepatitis, the HDV RNA PCR test will be part of a battery of tests that will be used to assess and monitor the clinical benefit of chronic treatment with HEPCLUDEX. If there is no publicly funded test to quantify viral load, clinicians cannot assess whether clinical benefit is observed, and by association determine improved clinical outcomes. Additionally, the practicality of the PBS restriction in practice is maximised if aligned with the CHB PBS restriction since patients with CHD are coinfectd with CHB and seen by the same physician who is highly experienced in the management of viral hepatitis and assessment of clinical benefit via CHB therapy on the PBS.</p>	<p>No.</p> <p><i>The commentary considered that alignment with the TGA proposed usage of bulevirtide is not appropriate when that usage is not cost-effective. Continuation and discontinuation criteria are used to restrict the eligible population for treatment to those who would most benefit and, thus, where there is the greatest value for money.</i></p>

MSAC issue to be addressed	How it is addressed in the resubmission	Was the issue addressed adequately? (as assessed by the commentary)
<p>Provide additional clarity around the likely pattern of testing and retesting as per the EASL guidelines to better inform the economic evaluation.</p> <p>[MSAC noted the EASL guidelines suggest criteria for continuation or discontinuation of treatment if undetectable HDV RNA occurs beyond one year, and retesting recommendations to monitor for relapse. (paragraph 7, page 5 of the PSD)]</p>	<p>No evidence was provided regarding a change in management based on the proportion of patients who had their treatment changed due to lack of clinical benefit. The economic evaluation assumed that all patients in the bulevirtide arm received 144 weeks of bulevirtide treatment, unless they experienced HBsAg seroclearance, disease progression or death. After Week 144, non-responders were assumed to cease treatment.</p>	<p>No.</p> <p><i>The commentary considered that there is little evidence (only four patients) that HDV RNA PCR testing will lead to a change in patient management.</i></p> <p><i>Aside from the modelled stopping rule for treatment in non-responders at Week 144 (which affected costs but not outcomes), the purpose of continued monitoring in the model was not clear.</i></p> <p><i>However refer to 'Summary of consideration and rationale for MSAC's advice'.</i></p>
<p>Identify and include any further new evidence of the test given the high risk of bias in the submitted evidence.</p> <p>[MSAC noted that the linked evidence for clinical effectiveness (test accuracy and performance, prognostic evidence and change in patient management) was considered at high risk of bias in all domains and its generalisability was uncertain as no Australian studies were included. There was no evidence presented for clinical utility or treatment effect variation. (paragraph 3, page 6 of the PSD)]</p>	<p>Addressed in Section 2</p> <p>Additional studies reporting on the prognostic value of testing and on the change in management following testing were included</p> <p>Search date: 2nd July 2024</p>	<p>Yes.</p> <p><i>However, the commentary considered that the additional studies provided no additional evidence on the prognostic value of a $>2 \log_{10}$ IU/mL decrease in HDV RNA and did not provide any new evidence of HDV RNA values influencing patient management.</i></p>
<p>Provide updated economic evaluation and financial assessments that address MSAC's advice.</p> <p>[MSAC noted that the only change in management that was modelled was to cease treatment in non-responders at week 96 (1.8 years). MSAC considered it likely that uptake and adherence to drug treatment had been overestimated by the ADAR, because drug administration is a daily injection for about 8 years. MSAC considered that the recommendations in the EASL guidelines on retesting had additional implications for the projected utilisation of the test that had not been captured in the economic model or the financial implications. (paragraph 3, page 7 of the PSD)]</p>	<p>The economic evaluation in the resubmission included cost for HDV RNA testing 6-monthly; but the only change in management that was modelled was to cease treatment in non-responders at week 144.</p> <p>The financial evaluation in the resubmission addressed most issues raised following the March 2024 submission.</p>	<p>No.</p> <p><i>The commentary considered that the purpose of continued monitoring in the economic model was not clear.</i></p> <p><i>The financial estimates are structurally sound but will require reassessment in light of any MSAC recommendations that change the frequency or duration of monitoring and its impact on the duration of treatment.</i></p>
Other issues of concern identified by the MSAC in the PSD:		
MSAC noted that standard practice is	This was not considered in the	No. This has not been addressed.

MSAC issue to be addressed	How it is addressed in the resubmission	Was the issue addressed adequately? (as assessed by the commentary)
if anti-HDV antibodies are detected, the patient should be tested for serum HDV RNA to determine whether an active infection is present – however there is currently no international standard for threshold levels of anti-HDV antibodies that are indicative of HDV exposure. There is also a lack of uniform international recommendations for screening for HDV infection in people with HBV. (paragraph 5, page 4 of the PSD)	resubmission.	
MSAC noted that HDV RNA levels are often very low and can be difficult to detect, although the sensitivity of available tests is improving. A 2016 international quality-control study showed a high variation in the detection and quantification of HDV RNA among assays, with consistent underestimations of the viral load. (paragraph 7, page 4 of the PSD)	This was not considered in the resubmission.	<i>No. However, reliability of the PCR tests to quantitate HDV RNA levels was addressed by the evaluation.</i>
MSAC considered that the test not being pathologist-determinable was appropriate. MSAC also considered that the MBS descriptor would appropriately specify the exclusion of patients with decompensated liver disease (Child Pugh B or C), as eligibility for treatment with bulevirtide is not being sought for these patient groups. (paragraph 2, page 5 of the PSD)	MBS item descriptor reflects that the test is not pathologist determinable.	Yes. <i>However, there were no restrictions on testing patients with decompensated liver disease (Child Pugh B or C) included.</i> <i>Note: This information is included in the PBS indication, so if patients are only being tested for access to bulevirtide this should exclude testing in patients with decompensated liver disease.</i>
MSAC agreed with ESC that codependency between testing and bulevirtide use had not been sufficiently established. MSAC considered it was unknown whether the level of HDV RNA (other than the presence of HDV RNA) would be used to alter patient management in non-responders or partial responders. (paragraph 5, page 6 of the PSD)	The claim of co-dependence will be met when HEPCLUDEX and the HDV RNA PCR test are both recommended and available on the PBS and MBS respectively. Further in order for continuation of HEPCLUDEX treatment (refer to both the PBAC and MSAC discussions on continuation of treatment in this resubmission), viral load reduction is required to be measured to ensure the patient is benefitting from treatment, and so there is co-dependence of the test with HEPCLUDEX for both establishing the presence of chronic HDV and the monitoring of viral load for continued treatment with HEPCLUDEX.	No. <i>The commentary considered that a claim of co-dependence is met when there is substantiation of bulevirtide treatment effect modification as a consequence of variation in a companion diagnostic biomarker (in this case HDV RNA). There has been no further discussion on the level of HDV RNA decline required at any time point to determine a treatment benefit or the likelihood of a having a sufficient response to reach the desired endpoint for obtaining a clinical benefit.</i> <i>However refer to 'Summary of consideration and rationale for MSAC's advice'.</i>
MSAC noted that the ADAR did not explore alternative scenarios of test and treatment provision. MSAC	Similar to the original submission, the resubmission did not explore alternative scenarios of test and	<i>No. This was not addressed in the resubmission.</i>

MSAC issue to be addressed	How it is addressed in the resubmission	Was the issue addressed adequately? (as assessed by the commentary)
considered that there may be benefits of testing, independent of treatment, given the prognostic information that HDV RNA testing may provide. MSAC noted that public consultation supported this approach at the PICO confirmation stage, yet the ADAR had not subsequently addressed it. (paragraph 2, page 7 of the PSD)	treatment provision.	
MSAC noted that patients entered the economic model at the point of treatment and considered that this was not its preferred approach as described in the MSAC Guidelines for submissions of codependent technologies, because it omits consideration of the impact of false results. (paragraph 3, page 7 of the PSD)	Addressed in Section 3 The resubmission presented a scenario analysis starting at the point of testing to explore the impact of false positive and false negative results on the ICER, by assuming 95% sensitivity and 95% specificity for HDV RNA testing at diagnosis to determine eligibility for starting bulevirtide treatment.	<i>Partially.</i> <i>The structure of the scenario analysis presented in the resubmission was fundamentally flawed as bulevirtide and BSC were compared in different populations (HDV RNA tested positive vs. tested negative). In addition, some of the assumptions used in the scenario analysis were not reasonable. A revised scenario analysis was conducted during the evaluation, with an ICER of \$95,000 to <\$115,000/QALY, compared with an ICER of \$95,000 to <\$115,000/QALY in the base case where 100% test accuracy was assumed.</i> <i>The implication of false results from the test to monitor treatment was not examined.</i>
MSAC also noted that there is high genetic variability among HDV genotypes, which can lead to underestimating the viral load. This can sometimes be by as much as >2 log ₁₀ , which is a clinically important difference. (paragraph 4, page 8 of the PSD)	<i>This was not considered in the resubmission.</i>	<i>No.</i>

Source: Table 1.2-1, page 9 of the resubmission; "Key aspects of the submission considered in April 2024 to be addressed for the MSAC" page v of the resubmission; the MSAC PSD for Application No. 1708.

ADAR = Applicant developed assessment report; CHB = chronic hepatitis B; CHD = chronic hepatitis D; EASL = European Association for the Study of the Liver; ESC = Evaluation Sub-committee; FN = false negative; FP = false positive; HBsAg = hepatitis B surface antigen; HCC = hepatocellular carcinoma; HDV = Hepatitis Delta Virus; ICER = incremental cost-effectiveness ratio; MBS = Medicare Benefits Schedule; MSAC = Medical Services Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PCR = polymerase chain reaction; PICO = Population, Intervention, Comparator, Outcomes; PSD = Public Summary Document; QALY = quality-adjusted life year; RNA = ribonucleic acid; VIDRL = Victorian Infectious Diseases Reference Laboratory.

Table 2 Key components of the clinical issue addressed by the resubmission

Component	Description
Population	Test: People diagnosed with chronic hepatitis B who have tested positive for serum anti-hepatitis D virus (anti-HDV) antibodies and are suspected of having chronic hepatitis D (CHD) Medicine: Patients with positive CHD with detectable polymerase chain reaction (PCR) results for serum/plasma HDV ribonucleic acid (RNA)
Prior tests	Diagnosis of HBV by hepatitis B surface antigen (HBsAg), Anti-HDV antibody testing
Intervention	Test: HDV RNA PCR on serum or blood Medicine: HEPCLUDEX (bulevirtide)
Comparator	Test: No HDV RNA testing Medicine: Symptomatic chronic HDV management
Clinical utility standard	Robogene® HDV RNA Quantification Kit 2.0 with a lower limit of detection (LLoD) of 6 IU/mL Test used in key clinical trial MYR301
Outcomes	Test: <ul style="list-style-type: none"> Concordance of the test with the clinical utility standard Predictive validity of the test (distinguished from HDV as a prognostic marker) Suitability of the test for monitoring (ability to distinguish response to treatment from background random variation, i.e. signal to noise ratio). Change in clinical management from initial and ongoing testing Medicine: <ul style="list-style-type: none"> Primary endpoint, composite endpoint at Week 48 of: <ul style="list-style-type: none"> Undetectable HDV RNA (HDV RNA < LLoD) or decrease in HDV RNA by $\geq 2 \log_{10}$ IU/mL from baseline, and ALT normalisation (i.e. below the central laboratory defined ULN). Secondary endpoints at Week 48 of: <ul style="list-style-type: none"> Undetectable HDV RNA at Week 48 ALT normalisation at Week 48 Proportions of patients achieving HDV RNA decrease by $\geq 2 \log_{10}$ IU/mL, Quality of life using EQ-5D, FSS and HQLQ Safety (adverse events, physical examinations, laboratory findings)
Clinical claims	In adults with chronic HDV infection, HEPCLUDEX (bulevirtide) is superior to current chronic HDV symptom management and is associated with a favourable safety profile. The MBS listing of HDV RNA PCR testing and the PBS listing of HEPCLUDEX (bulevirtide) for the diagnosis and the treatment of chronic HDV will result in superior health outcomes compared to no testing and no access to HEPCLUDEX.

Source: Table 1.1-1, p3 of the resubmission

ALT = Alanine Aminotransferase; CHD = Chronic Hepatitis D; EQ-5D = EuroQol 5-Dimensions; FSS = Fatigue Severity Scale; HBV = Hepatitis B Virus; HBsAg = Hepatitis B Surface Antigen; HDV = Hepatitis Delta Virus; HQLQ = Hepatitis Quality of Life Questionnaire; LOD = Limit of Detection; LLoD = Lower Limit of Detection; MBS = Medical Benefits Schedule; PCR = Polymerase Chain Reaction; PBS = Pharmaceutical Benefits Scheme; RNA = Ribonucleic Acid; ULN = Upper Level of Normal.

Note: Blue shading indicates components and descriptions unchanged from the previous submission.

5. Prerequisites to implementation of any funding advice

The TGA granted HEPCLUDEX Priority Review Determination and Orphan Drug Designation on 15th March 2023. The TGA Priority Review dossier for HEPCLUDEX was lodged on the 15 March 2023. The Australian Register of Therapeutic Goods (ARTG) registration commenced 30 July 2024, as the date of first approval. The approved TGA indication is as follows:

HEPCLUDEX is indicated for the treatment of chronic hepatitis delta virus (HDV) infection in adults with compensated liver disease.

In Australia, the only HDV RNA PCR test currently available is an in-house assay developed by the Victorian Infectious Disease Reference Laboratory (VIDRL), which is accredited by the National Association of Testing Authorities (NATA). The commentary noted that the test is a Class 3 in-house in vitro diagnostic (IVD) and therefore does not need to be included in the ARTG, although

Class 3 IVDs do require NATA accreditation and need to meet the National Pathology Accreditation Advisory Council (NPAAC) standards.

6. Proposal for public funding

The proposed new MBS listing (as per the ratified PICO confirmation) is shown in Table 1. *This has not changed from the previous submission.* The test proposed is an in vitro diagnostic test which measures the amount of HDV RNA present in the blood. If HDV RNA is detected, then the patient is considered to have a current Hepatitis D infection and may be eligible for bulevirtide (if other clinical criteria are also met). The test is also proposed for monitoring the effectiveness of treatment, however no separate treatment continuation criteria were proposed in the PBS restrictions.

Table 1 Newly proposed MBS item for testing HDV RNA

	Category 6 – PATHOLOGY SERVICES Group P3 - Microbiology
MBS item *XXXX	
Quantitation of Hepatitis D viral RNA load in plasma or serum in:	
a) The pre-treatment evaluation for access to therapy for chronic HDV in patients who are Hepatitis D viral antibody positive and suspected of having chronic hepatitis D; or	
b) A patient undertaking viral therapy for chronic hepatitis D with bulevirtide for the purpose of assessing treatment effectiveness.	
To a maximum of 2 tests in a 12 month period	
Fee: \$152.10 Benefit: 75% \$114.10 85% = \$129.30	

PASC agreed that the fee was reasonable for HDV RNA PCR testing in Australia. The wording and fee are consistent with MBS item 69482 for hepatitis B viral DNA testing. MSAC considered that “the test not being pathologist-determinable appeared appropriate.”

In the PSD, MSAC considered that:

- “testing may potentially have prognostic value independent of its use for access to bulevirtide, although this had not been claimed in the submission.”

This was not further explored in the resubmission.

- “the MBS descriptor should appropriately specify the exclusion of patients with decompensated liver disease (Child Pugh B or C), as eligibility for treatment with bulevirtide is not being sought for this patient group.”

This was not discussed in the resubmission.

Note: This information is included in the PBS indication, so if patients are only being tested for access to bulevirtide this should exclude testing in patients with decompensated liver disease.

- “there would be no need for a practice note to provide clinical guidance on determination of Hepatitis D chronicity as it is very unlikely in practice that cases of acute infection would be detected by an HDV RNA test.”
- in response to the ESC recommendation to futureproof the item descriptor, MSAC considered that as “there were presently no other equivalent medications under consideration, there was no current need to amend the descriptor to refer to PBS-listed chronic hepatitis D treatments in general.”

7. Population

There are two populations proposed for HDV RNA PCR testing:

1. Patients who are hepatitis B surface antigen (HBsAg) positive and anti-HDV antibody positive (where testing is performed to confirm the diagnosis of CHD infection status and assist in determining eligibility for bulevirtide); and
2. Patients undertaking antiviral therapy for CHD with bulevirtide to measure the clinical benefit of treatment.

This is the same as for the previous submission considered by MSAC in April 2024. PASC had agreed that these populations were appropriate testing populations. The purpose of the second population is to assess treatment response.

Prevalence of HDV

A study by Wong et al. (2024)¹, that was identified during the commentary's evaluation, conducted a meta-analysis to estimate the prevalence of HDV in CHB populations in many countries, including Australia. The pooled HDV prevalence estimates were calculated using fixed effect (FE) meta-analyses. The Australian estimate was based on the three studies used to estimate the prevalence in the previous submission. The prevalence of CHB in Australia was estimated to be 0.37% (95% CI 0.36, 0.37), and it was estimated that 4.1% (95% CI 3.65, 4.54) of individuals with CHB had HDV. However, these updated estimates do not include any new data from recently published Australian studies and may not reflect the true prevalence of HDV in Australia due to lack of ascertainment.

In the PSD for 1708, MSAC agreed that “the prevalence of HDV is likely to be low in Australia due to high rates of vaccination against HBV, but prevalence is likely to be much higher in high-risk populations, such as people born overseas, people from culturally and linguistically diverse backgrounds, people who inject drugs, and/or in men who have sex with men.”

8. Comparator

There was no change from the previous submission in the proposed comparator of 'no HDV RNA PCR testing'. The commentary noted that this comparator is appropriate.

9. Summary of public consultation input

Consultation input was welcomed for MSAC Application 1708 from three professional organisations, three consumer organisations, and one individual, who was a medical professional.

The five organisations that submitted input were:

- Australian Pathology (AP)
- Gastroenterological Society of Australia (GESA)
- Hepatitis SA
- Hepatitis Queensland (HQ)
- Public Pathology Australia (PPA)

¹ Wong, RJ, Brosgart, C, Wong, SS, Feld, J, Glenn, J, Hamid, S, Cohen, C, Zovich, B, Ward, J, Wedemeyer, H, Yurdaydin, C and Gish, R 2024a, 'Estimating the prevalence of hepatitis delta virus infection among adults in the United States: A meta-analysis', *Liver Int*, vol. 44, no. 7, pp. 1715-1734.

- Hepatitis NSW

Upon resubmission for MSAC Application 1708.1, consultation input was received from four consumer groups or organisations and two medical, health, or other (non-consumer) organisations.

The organisations that submitted input were:

- Roche Diagnostics Australia
- Hepatitis SA
- Hepatitis NSW
- Hepatitis Australia
- Gastroenterological Society of Australia (GESA)
- Liver Foundation

Level of support for public funding

All organisations were supportive of the public funding of this service.

Comments on PICO

- Roche Diagnostics Australia, Liver Foundation, and Hepatitis NSW considered the proposed population and proposed approach appropriate.
- In terms of the proposed approach, GESA noted that without Medicare reimbursement for HDV RNA testing, hepatitis D testing uptake will remain very low. GESA also stated that no additional management beyond the HDV RNA test is required, and for those who are shown to have only past infection, management costs for hepatitis D and related liver cancer surveillance can be avoided.
- Roche Diagnostics Australia agreed the comparator accurately reflected Australian practice, noting that while HDV RNA PCR testing is not currently standard practice, it is recommended in both relevant RACGP and GESA recommendations.
- GESA agreed with the outcomes set out in the PICO. Roche Diagnostics Australia partially agreed with the outcomes in the PICO, adding that diagnosis of HDV infection via RNA PCR testing should be considered as an outcome, noting the benefits for patients through increased confidence in accuracy of diagnosis, without the risk of liver biopsy to confirm current HDV infection.

Perceived Advantages

Advantages of the service noted by organisations included:

- Enhanced diagnostic accuracy, noting that unlike current testing (serology), which does not distinguish between current and past infections, RNA PCR testing has increased accuracy in diagnosing HDV, including quantifying virus levels and determining active and past infections.
- Enhancing the streamlining of treatment pathways.
- Facilitating improved health outcomes through enhanced access to effective treatment, reducing disease burden and long-term health implications, reducing morbidity and mortality.
- Early detection of HDV, allowing timely initiation of treatment.
- Improved monitoring of disease progression, ensuring patients receive appropriate care.
- Prevention of unnecessary medical interventions and better allocation of healthcare resources.

- Greater access for those with dual chronic conditions of HBV and HDV, which are associated with faster disease progression than HBV mono-infection, as well as alleviate current underdiagnosis or late diagnosis of HDV.

Support for Implementation /issues

- Roche Diagnostics Australia recommended that MSAC consider an item descriptor that allows for:
 - The use of an RNA PCR test to confirm HDV infection (either chronic or acute) as part of diagnosis (e.g., without a specific requirement to consider antiviral therapy).
 - The use of an RNA PCR test to test for monitoring of treatment response to PBS-listed therapy.
- Roche Diagnostics Australia and GESA agreed with the proposed fee.
- Liver Foundation noted the expected effect of the proposed application as prolonged life, avoiding new cases of advanced liver disease and primary liver cancer. Hepatitis NSW stated expected effects included enhanced disease monitoring, early treatment facilitation, and reduced burden of chronic hepatitis D.
- Roche Diagnostics Australia encouraged MSAC to consider supporting RNA PCR testing for HDV independently of PBAC recommendation for bulevirtide.
- Roche Diagnostics Australia noted that inclusion of the service on the MBS will enable relatively rapid implementation of the service, due to tests being able to be implemented by multiple pathology providers using existing equipment.
- GESA noted that information about the public funding of this service could be encompassed into the National hepatitis B testing policy and Australian Consensus statement on the management of hepatitis B, which are being updated in 2025.
- Hepatitis NSW and Hepatitis Australia noted it is important to ensure that general practitioners play a role in requesting HDV RNA PCR testing, to monitor response to the proposed treatment (bulevirtide). This is essential for the following reasons:
 - Access to HDV RNA PCR testing for people living with hepatitis B in rural and regional areas, who may have difficulties accessing specialists.
 - Access to HDV RNA PCR testing for people living with hepatitis B and under the care of a GP rather than a specialist, or in a shared care arrangement
 - Allowing GPs to request HDV RNA PCR testing in this instance could expedite diagnosis and access to care.

10. Characteristics of the evidence base

The approach taken in the resubmission was to present updated evidence on the use of bulevirtide to reduce the quantity of HDV RNA and alanine aminotransferase (ALT) in people with detectable HDV RNA prior to treatment. The aim was to link these data with evidence that those people with undetectable HDV RNA have a better prognosis than those with detectable HDV RNA. The evidence presented in the resubmission is summarised in Table 2.

The commentary considered that the presented linked evidence approach addressed most parts of the analytic framework. However, the commentary concluded that there was limited evidence to determine whether HDV RNA levels will result in a change in management for any patients and there was no evidence demonstrating health benefits associated with any change in management.

Table 2 Summary of the linked evidence approach

	Type of evidence supplied	Extent of evidence supplied	Overall risk of bias
Accuracy and performance of the test (cross-sectional accuracy)	Concordance of quantitative HDV RNA levels between different tests and RNA extraction methods.	☒ k=3 n=335	High
Prognostic evidence (longitudinal accuracy)	Comparison of outcomes in patients receiving <i>usual care</i> , conditioned on the presence, absence or reduction of HDV RNA at baseline	☒ k=14 retrospective cohorts n=2,749 ☒ k=2 prospective studies n=154 ☒ k=1 systematic review n=4,853	High
Predictive effect	Comparison of outcomes in patients receiving usual care, conditioned on the reduction of HDV RNA	☒ k=5 retrospective cohorts n=244	High
Change in patient management	Evidence to show that HDV RNA test results guide decisions about stopping treatment (due to response or lack of response) or intensifying treatment (due to limited response)	☒ k=2 uncontrolled before/after studies n=129	High
Health outcomes (clinical utility)	No evidence presented.	☐ k=0 n=0	
Predictive effect (treatment effect variation)	No evidence presented	☐ k=0 n=0	
Treatment effect (enriched)	Single randomised controlled trial of bulevirtide vs symptom management of CHD in patients that are tested for HDV RNA by PCR in both arms and found to be positive.	☒ k=1 n=150	Low

Source: Table compiled during the evaluation

CHD = Chronic Hepatitis D; HDV = Hepatitis D Virus, k=number of studies, n=number of patients, NA=not applicable; RNA = Ribonucleic Acid

Note: Blue shading denotes clinical evidence unchanged from the previous submission.

Note: Data of treatment effect provided in the resubmission was from the same key trial (MYR301) used in the previous submission, but the data provided in the resubmission covered a longer treatment duration (up to 144 weeks) compared to 96 weeks in the previous submission.

11. Comparative safety

No claims were made about the safety of HDV RNA PCR testing in the previous submission or in the resubmission.

Adverse events from testing

As discussed in the Commentary of the previous submission, testing is performed on serum or blood. It is unlikely that any physical harms would result directly from the test itself, although there may be psychological harms from a diagnosis or incorrect diagnosis. Blood tests would be necessary for repeat testing, which can lead to the adverse events associated with diagnostic venepuncture, such as vasovagal reactions, pain and bruising, and nerve injuries.

Adverse events from changes in management

The incidence of drug-related or treatment-emergent adverse events (TEAEs) was significantly higher in patients treated with bulevirtide 2 mg once daily than in the comparator arm receiving best supportive care (49.0% vs. 0%) during the first 48 weeks, although the proportion of patients experiencing at least one TEAE was comparable between the two arms (83.7% vs. 76.5%) during this time period. Continued exposure to the study drug resulted in higher proportions of treated patients experiencing any TEAEs. The AEs reported in MYR301 in the entire 144 weeks of treatment were mostly Grade 1 (mild) or 2 (moderate) in severity. No TEAEs resulted in a change in management, i.e. premature discontinuation of study drug.

12. Comparative effectiveness

The updated literature search undertaken in the resubmission identified four additional studies reporting on the prognostic value of HDV RNA PCR testing to determine viral load and one study reporting on a potential change in management was included in the analysis during evaluation.

An independent literature search conducted during evaluation found an additional three small studies reporting on the accuracy of the test, and a systematic review reporting on the association between HDV RNA detection and liver morbidity and mortality.

Where appropriate, studies providing evidence from the previous submission were also included in the evaluation.

The available data differed from the previous submission, as indicated in Table 3.

Table 3 Data availability to inform comparisons

Proposed test vs no test	<i>No evidence presented</i>	
Proposed test vs alternative test	<i>3 additional small studies reporting concordance of quantified HDV RNA results</i>	
	Proposed drug	Comparator drug
Biomarker test positive	<i>Updated data from MYR301</i>	<i>Updated data from MYR301</i>
Biomarker test negative	<i>No evidence presented</i>	<i>No evidence presented</i>

Source: Table compiled during the commentary's evaluation.

The populations and tests were largely transferable across the linked evidence but the treatment regimens identified in the literature searches largely involved treatment with interferon (IFN), which is not used in Australia for CHD.

The overall risk of bias in the treatment effect trial (MYR301) was considered low by the commentary. The limitation of the MYR301 trial design was the open-label design of the study, in which patients and investigators were not blinded to the treatment group assignment. The risk of bias was considered low for the efficacy endpoints (i.e., serum HDV RNA level and ALT level), as they were objective outcomes and those who assessed these endpoints were blinded to treatment allocation. However, there is potential for bias in assessment of patient reported outcomes such as adverse events (AEs) and quality of life.

Comparative accuracy/test performance

This section was unchanged in the resubmission, *but additional evidence was identified during the evaluation.*

The clinical utility standard used in the previous submission, the RoboGene HDV RNA Quantification kit 2.0, is still considered to be the appropriate clinical utility standard in the resubmission.

The proposed test, HDV RNA PCR testing, is an in vitro diagnostic test currently performed by only one laboratory in Australia: The Victorian Infectious Disease Reference Laboratory (VIDRL). This test is NATA accredited. All samples in Australia would need to be sent to the VIDRL for processing. In future, more laboratories in Australia may start offering this test. *This is unchanged from the previous submission.*

The VIDRL currently uses an in-house assay **redacted** that measures the amount of HDV RNA present in blood and detects all known HDV genotypes. **redacted**

One recent study² compared the accuracy of 2 commercially available kits, Vircell Hepatitis Delta RT-PCR system kit and EurobioPlex HDV assay, with the clinical utility standard, the RoboGene HDV RNA Quantification kit 2.0, using 150 HBsAg positive samples (90 HDV-RNA negative and 61 HDV-RNA positive).

The qualitative concordance, defined as the number of patients correctly identified as having either detectable or undetectable HDV, i.e. having a positive or negative result, was 100%. This was similar to the qualitative concordance between the VIDRL in-house test and the RoboGene clinical utility standard, which had **redacted** positive percent agreement, and **redacted** negative percent agreement (as reported by Bonanzinga (2023)³ in the previous submission). **redacted**

The quantitative concordance, defined as the ability of the tests to reliably detect a similar viral load for each HDV positive patient, was less consistent. The Vircell kit and the EurobioPlex assay overestimated the viral load by 0.98 log₁₀ IU/mL and 1.46 log₁₀ IU/mL, respectively, and the RoboGene kit underestimated it by 0.98 log₁₀ IU/mL. Again Bonanzinga (2023) **redacted**

A recent review of HDV RNA assays⁴, identified during evaluation, provided a summary of the factors that result in variability in the performance characteristics of different quantitative HDV RNA assays. These include:

- RNA extraction methodology

Two studies⁵ found that the result was significantly influenced by the extraction method used. Automated extraction significantly underestimated the viral load by approximately 1 log₁₀ IU/mL compared with manual extraction.

A third study⁶ found that viral load estimates using automated extraction methods led to 6- to 10-fold lower HDV RNA values when compared with manual RNA extraction.

² Illescas-López, M, Chaves-Blanco, L, de Salazar, A, Hernández-Febles, M, Carracedo, R, Lagarejos, E, Fuentes, A, Pereira, S, Cea, M, De La Iglesia, A, Freyre, C, Iborra, A, Odero, V, García-Barrionuevo, A, Aguilera, A, Pena, MJ and García, F 2024, 'Assessment of performance and comparison of three commercial HDV RNA detection assays: implications for diagnosis and treatment monitoring', Front Cell Infect Microbiol, vol. 14, p. 1422299.

³ Bonanzinga S. HDV Robogene Verification: Victorian Infectious Disease Reference Laboratory 2023.

⁴ Wedemeyer, H, Leus, M, Battersby, TR, Glenn, J, Gordien, E, Kamili, S, Kapoor, H, Kessler, HH, Lenz, O, Lütgehetmann, M, Mixson-Hayden, T, Simon, CO, Thomson, M, Westman, G, Miller, V, Terrault, N and Lampertico, P 2023b, 'HDV RNA assays: Performance characteristics, clinical utility, and challenges', Hepatology.

⁵ Anolli, MP, Renteria, SU, Degasperis, E, Borghi, M, Facchetti, F, Sambarino, D, Perbellini, R, Monico, S, Ceriotti, F and Lampertico, P 2024, 'Quantification of serum HDV RNA by Robogene 2.0 in HDV patients is significantly influenced by the extraction methods', Liver Int, vol. 44, no. 3, pp. 831-837.

Sandmann, L, Bremer, B, Deterding, K, Port, K, Gey, B, Früchtel, C, Reinhardt, A, Lachmann, I, Cornberg, M, Kefalakes, H, Maasoumy, B and Wedemeyer, H 2024, 'Letter to the Editor: The WHO HDV RNA international standard does not reflect variability of real-world samples', Hepatology.

⁶ Bremer, B, Anastasiou, OE, Ciesek, S and Wedemeyer, H 2019, 'Automated nucleic acid isolation methods for HDV viral load quantification can lead to viral load underestimation', Antivir Ther, vol. 24, no. 2, pp. 117-123.

- Primer/probe design

A study reporting on the first international external quality control assessment for HDV RNA quantification in plasma from 28 laboratories in 17 countries worldwide⁷ found that thirteen labs (46.3%) properly quantified all 18 positive samples, 16 (57.1%) failed to detect between one and 10 samples, and several others underestimated ($>3 \log_{10}$ IU/mL) the viral load of African genotype strains (1 and 5-8). The discrepancies in this study were mostly attributed to primer/probe mismatches related to the high genetic variability of HDV.

- Overall, there was a dearth of standardisation and well-characterised sample evaluation panels across testing laboratories

One study⁸ reported on the use of correction factors to ensure reliable quantification of HDV between laboratories. The authors noted that the RoboGene HDV RNA Quantification Kit 2.0 has only been validated with the INSTANT Virus RNA/DNA Kit, a manual nucleic acid extraction assay. However, most of the routine diagnostic laboratories use automated extraction systems to decrease hands-on time per sample and increase assay performance. The authors suggest that any modification of a validated extraction and amplification/detection protocol requires determination of a protocol specific correction factor.

Three studies found that the quantitative differences between tests could potentially result in inappropriate changes in management.

- One study⁹ suggested that the extraction method used in the diagnostic laboratory may influence the clinician's decision on whether to continue treatment in patients achieving undetectable HDV RNA during or after treatment. The concerns related to automated extraction but not with manual extraction.
- Another study¹⁰ found that the difference in viral load detected led to misclassification of two on-treatment samples with low viral load. They were found to be false negative with one of the automated extraction methods and could potentially affect clinical management decisions.
- An Australian study¹¹ found that 4 out of 22 positive samples showed a difference of $>1 \log_{10}$ IU/mL between the VIDRL in-house HDV RNA test and the RoboGene HDV RNA Quantification kit 2.0. One sample showed a difference of $>2 \log_{10}$ IU/ml and could potentially affect the clinical management of these patients.

In summary, these data strongly suggest that the methods used in Australia for RNA extraction and HDV PCR testing, once more laboratories in addition to the VIDRL offer this service, should be closely monitored and standardised with an effective Quality Assurance Program (QAP) to ensure reliability when determining the viral load. The method currently used by the VIDRL for RNA extraction was not mentioned in the resubmission, or in the previous submission.

⁷ Le Gal, F, Brichler, S, Sahli, R, Chevret, S and Gordien, E 2016, 'First international external quality assessment for hepatitis delta virus RNA quantification in plasma', *Hepatology*, vol. 64, no. 5, pp. 1483-1494.

⁸ Stelzl, E, Ciesek, S, Cornberg, M, Maasoumy, B, Heim, A, Chudy, M, Olivero, A, Miklau, FN, Nickel, A, Reinhardt, A, Dietzsch, M and Kessler, HH 2021, 'Reliable quantification of plasma HDV RNA is of paramount importance for treatment monitoring: A European multicenter study', *J Clin Virol*, vol. 142, p. 104932.

⁹ Anolli, MP, Renteria, SU, Degasperis, E, Borghi, M, Facchetti, F, Sambarino, D, Perbellini, R, Monico, S, Ceriotti, F and Lampertico, P 2024, 'Quantification of serum HDV RNA by Robogene 2.0 in HDV patients is significantly influenced by the extraction methods', *Liver Int*, vol. 44, no. 3, pp. 831-837.

¹⁰ Bremer, B, Anastasiou, OE, Ciesek, S and Wedemeyer, H 2019, 'Automated nucleic acid isolation methods for HDV viral load quantification can lead to viral load underestimation', *Antivir Ther*, vol. 24, no. 2, pp. 117-123.

¹¹ Bonanzinga, S 2023, HDV Robogene Verification, Victorian Infectious Disease Reference Laboratory.

Prognostic evidence

The prognostic effect of detectable versus undetectable HDV RNA at baseline

A recently published systematic review and meta-analysis¹², identified during evaluation of the resubmission, on the association between HDV RNA detection and liver morbidity and mortality in patients with CHB/CHD, showed statistically significant associations for all the outcomes investigated (Table 4). When the source of the results (baseline detectable/undetectable HDV RNA or post-treatment status) were taken into account, the hazard ratios (HRs) indicate that detecting HDV RNA at baseline in patients with CHB/CHD is prognostic of worse outcomes compared with having undetectable HDV RNA, especially for any liver-related event, cirrhosis, hepatocellular carcinoma (HCC), and mortality outcomes.

Table 4 Association between HDV status and subsequent health outcomes

Study	Follow-up	Included studies	Liver related events
Gish et al. (2024)	Range 3-19.4 years	<p>Jang et al. (2021) Meta-analysis (MA) used baseline (B) values, but included 1,300 HDV Ab neg patients</p> <p>Kamal et al. (2020) MA used B values</p> <p>Palom et al. (2020) MA used B values</p> <p>Romeo et al. (2009) Uncertain if values used in MA were B or post-treatment (PT), numbers do not align with the study text.</p> <p>Romeo et al. (2014) MA used PT values</p> <p>Roulot et al. (2020) MA used B +/- PT values</p> <p>Wanke et al. (2017) MA used B +ve/-ve patient numbers, but post-treatment HR values</p> <p>Wanke et al. (2020) MA used PT values, but not all patients were included</p> <p>Scheller et al. (2021) MA used PT values</p> <p>Spaan et al. (2020) MA used B values</p> <p>Yurdaydin et al. (2018) MA used PT values</p>	<p><u>Any liver--related event</u> RR=1.48 (95% CI 0.93, 2.33) k=3 (2 PT, 1 B) HR=2.62 (95% CI 1.55, 4.44) k=7 (3 PT, 4 B)</p> <p><u>Cirrhosis</u> RR=1.74 (95% CI 1.24, 2.45) k=2 (1 B, 1 uncertain) HR=5.75 (95% CI 3.67, 9.03) k=1 (B)</p> <p><u>DC</u> RR=2.28 (95% CI 1.40, 3.71) k=1 (uncertain) HR=3.82 (95% CI 1.60, 9.10) k=4 (2 PT, 2 B)</p> <p><u>HCC</u> RR=1.34 (95% CI 0.74, 2.43) k=1 (uncertain) HR=2.97 (95% CI 1.87, 4.70) k=5 (1 PT, 4 B)</p> <p><u>Liver transplant</u> HR=7.07 (95% CI 1.61, 30.99) k=2(1 PT, 1 B)</p> <p><u>Mortality</u> RR=3.22 (95% CI 2.06, 5.04) k=1 (uncertain) HR=3.78 (95% CI 2.18, 6.56) k=4 (1 PT, 3 B)</p>

Source: Table compiled during the evaluation.

Significant differences are highlighted in boldface.

B= baseline; CI = confidence interval; DC = decompensated cirrhosis; HCC = hepatocellular carcinoma; HDV = hepatitis D virus; HR = hazard ratio; MA = meta-analysis; PT= post-treatment; RNA = ribonucleic acid; RR = relative risk.

The three recent studies identified by the resubmission also showed a statistically significant difference in the proportion of patients with detectable versus undetectable HDV RNA at baseline having liver-related events, favouring those with undetectable HDV RNA.

The MA for any liver-related outcome, conducted by Gish et al. (2024)¹³ was repeated during the commentary's evaluation including only those studies reporting HR values for baseline detectable versus undetectable HDV RNA. The study by Wranke et al. (2024)¹⁴ was also included

in the MA as it provided appropriate data. The pooled HR value (3.66; 95% CI 1.13, 6.20) indicates that patients with detectable HDV RNA at baseline are significantly more likely to have a liver-related adverse event than those with undetectable HDV RNA at baseline (Figure 1).

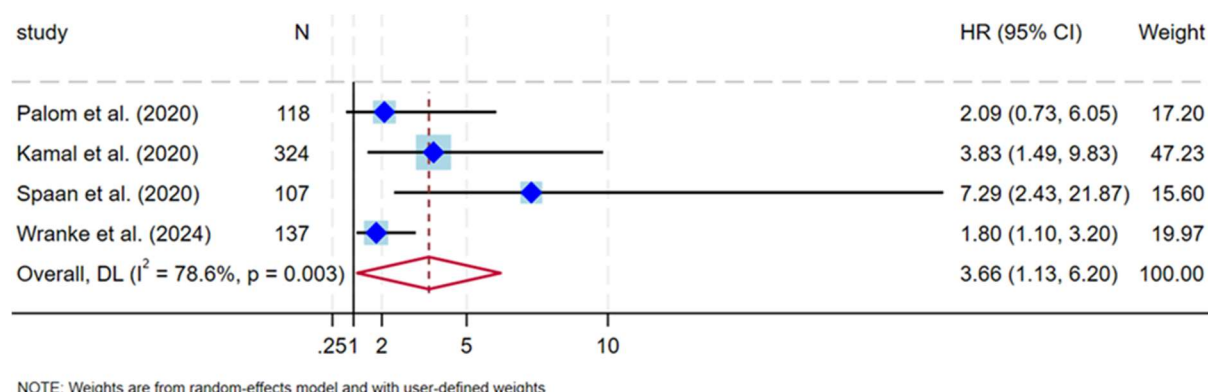


Figure 1 MA of studies comparing any liver-related outcome for patients with detectable versus undetectable HDV RNA at baseline.

Source: constructed during the commentary's evaluation

The prognostic effect of higher versus lower HDV RNA levels at baseline

Two of the four studies identified by the resubmission showed a statistically significant difference in the proportion of patients above and below specific HDV RNA values having liver-related events, favouring those with lower levels of HDV RNA. One study with a high risk of bias found that patients with baseline HDV RNA levels >1000 IU/ml at baseline were more likely to have a serious liver-related event or death than those with lower HDV RNA levels (HR=2.87, 95% CI 1.60, 5.13, $p < 0.001$)¹⁵. A second study with a moderate risk of bias used a receiver operating characteristic (ROC) curve analysis to assess the ability of HDV RNA to predict the development of cirrhosis in 193 HDV RNA positive patients¹⁶. The authors found that patients with >5.78 log₁₀ HDV RNA (i.e. approximately 600,000 copies/mL) were more likely to develop cirrhosis than those with lower levels.

The association between an undetectable viral load during follow-up or before study endpoint and subsequent clinical outcomes

Seven studies reported on the likelihood of having a liver-related event in treatment responders compared to non-responders. The treatments included in these studies were mostly interferon-based; no study used bulevirtide. In these studies responders were all defined as having sustained (at least 6 months) undetectable HDV RNA results. All seven studies reported fewer

¹² Gish, RG, Wong, RJ, Di Tanna, GL, Kaushik, A, Kim, C, Smith, NJ and Kennedy, PTF 2024, 'Association of hepatitis delta virus with liver morbidity and mortality: A systematic literature review and meta-analysis', *Hepatology*, vol. 79, no. 5, pp. 1129-1140.

¹³ Gish RG, Wong RJ, *et al.*. Association of hepatitis delta virus with liver morbidity and mortality: A systematic literature review and meta-analysis. *Hepatology (Baltimore, Md)*. 2024;79(5):1129-40.

¹⁴ Wranke A, Lobato C, *et al.* Long-term outcome of hepatitis delta in different regions world-wide: Results of the Hepatitis Delta International Network. *Liver Int*. 2024;44(9):2442-57.

¹⁵ d'Arminio Monforte, A, Tavelli, A, Salpini, R, Piermatteo, L, D'Anna, S, Carrara, S, Malagnino, V, Mazzotta, V, Brancaccio, G, Marchetti, GC, Rosselli Del Turco, E, Rossotti, R, Mussini, C, Antinori, A, Lo Caputo, S, Ceccherini Silberstein, F, Gaeta, GB, Svicher, V, Puoti, M and Group, for the ICONA Foundation Study Group 2024, 'Determinants of worse liver-related outcome according to HDV infection among HBsAg positive persons living with HIV: Data from the ICONA cohort', *Liver International*, vol. 44, no. 2, pp. 603-613.

¹⁶ Romeo, R, Foglieni, B, Casazza, G, Spreafico, M, Colombo, M and Prati, D 2014, 'High serum levels of HDV RNA are predictors of cirrhosis and liver cancer in patients with chronic hepatitis delta', *PLoS One*, vol. 9, no. 3, p. e92062.

clinical events in responders compared with non-responders, reaching statistical significance in six out of seven studies.

Five studies reported on patients who were always positive for HDV RNA and compared these with those who became negative during follow-up, either by responding to treatment or spontaneously clearing the virus. All five studies reported fewer clinical events in patients who became HDV RNA negative during follow-up compared with those who remained positive. The findings were statistically significant for at least one outcome in three of the five studies.

The MA for any liver-related outcome, conducted by Gish et al. (2024) was repeated during the commentary's evaluation including only those studies reporting HR values for post-treatment detectable versus undetectable HDV RNA. The study by Wranke et al. (2024) was also included in the MA as it provided appropriate data. The pooled HR value (2.22; 95% CI 1.20, 3.25) indicates that patients with detectable HDV RNA after treatment are significantly more likely to have a liver-related adverse event than those with undetectable HDV RNA after treatment (Figure 2).

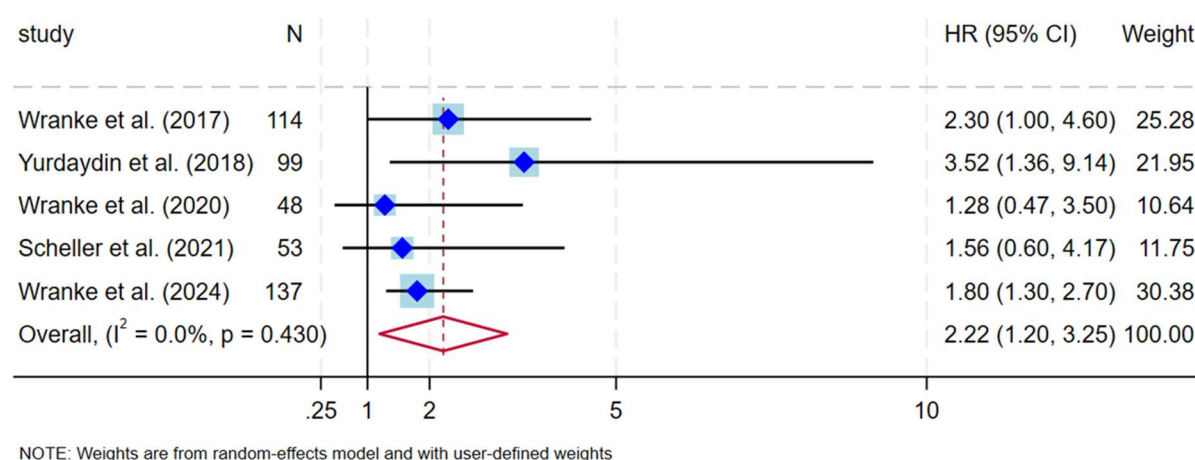


Figure 2 MA of studies comparing any liver-related outcome for patients with detectable versus undetectable HDV RNA post-treatment.

Source: constructed during evaluation

The association between a $>2 \log_{10}$ IU/mL decline in HDV RNA and clinical outcomes

Three studies provided subgroup analyses assessing clinical outcomes among patients with a $>2 \log_{10}$ IU/mL reduction in viral load compared to those with a smaller or no reduction in viral load (Table 5).

Table 5 Response to treatment with a HDV RNA decrease of $>2 \log_{10}$ in viral load and subsequent health outcomes

Study	Follow-up	Population	Any liver related event
<i>Farci et al. (2004)</i>	12 years	N=41 patients with CHD treated with 9 million or 3 million U of IFN or no treatment	<p>9 million U IFN:</p> <p>Change in HDV RNA load $>2 \log_{10}$ copies/mL</p> <p>Change in activity grade/fibrosis scores* compared to no treatment $-4.7 \pm 2.9, p=0.0004; -2.0 \pm 1.9, p=0.007$</p> <p>3 million U IFN:</p> <p>Change in HDV RNA load $\sim 1 \log_{10}$ copies/mL</p> <p>Change in activity grade/fibrosis scores* compared to no treatment $-0.5 \pm 5.2, NS; -0.7 \pm 1.5, NS$</p> <p>None:</p> <p>Change in HDV RNA load $\sim 1 \log_{10}$ copies/mL</p>
<i>Palom et al. (2021)</i>	Mean 5.6 years (range 3-16)	<p>N=56 CHD patients with detectable HDV RNA and followed for >3 years</p> <p>Patients had been treated with IFN or NA</p> <p>14 had a $\geq 2 \log_{10}$ HDV RNA decline, including 11 who became undetectable</p> <p>42 had unchanged HDV RNA levels</p>	<p>With and without a $\geq 2 \log_{10}$ HDV RNA decline</p> <p>Any liver-related clinical event: $p=0.132$</p> <p>Liver decompensation or HCC $p=0.378$</p>
<i>Wranke et al. (2020)</i>	Median 5.9 years (range 1.6-13.4)	<p>N=90 patients HDV RNA positive at baseline who were assigned to 3 different 48-week treatment strategies</p> <p>Group 1: n=31 PEG-IFN plus ADV</p> <p>Group 2: n=29 PEG-IFN plus placebo</p> <p>Group 3: n=30 ADV alone</p> <p>22 patients were HDV RNA negative at last follow-up</p>	<p>Association of HDV-RNA decline (vs no decline) and the development of clinical endpoints (death, liver transplantation or hepatic decompensation)</p> <p>$>2 \log_{10}$ HDV RNA decline week 24 $p=0.77$</p> <p>$>1 \log_{10}$ HDV RNA decline at end of treatment</p> <p>clinical endpoints: 6/27 (22%) vs 6/33 (18%)</p> <p>$RR=1.22$ (95% CI 0.44, 3.36) $p=0.47$</p> <p>$>2 \log_{10}$ HDV RNA decline at end of treatment</p> <p>clinical endpoints: 4/17 (24%) vs 8/43 (19%)</p> <p>$RR=1.27$ (95% CI 0.44, 3.65) $p=0.32$</p> <p>$>2 \log_{10}$ HDV RNA decline at week 72 or end of follow-up $p=0.11$</p>

Source: Table compiled during the evaluation.

*For each liver biopsy specimen, stage of fibrosis and grade of activity were established as follows:

- Fibrosis was scored on a scale of 0 to 4, with 0 indicating absence of fibrosis, 1 fibrous portal expansion, 3 bridging fibrosis, and 4 cirrhosis.
- The intensity of the necroinflammatory lesions was measured by grade of activity, which comprised the sum of 3 scores, including interface hepatitis Π bridging necrosis (0–10), lobular necrosis and inflammation (0–4), and portal inflammation (0–4).

ADV = adefovir; CI = confidence interval; HCC = hepatocellular carcinoma; HDV = hepatitis D virus; IFN = interferon; NA= nucleos(t)ide analogues; PEG = pegylated; RNA = ribonucleic acid; RR = relative risk; U = units.

Of the three studies reporting on the prognostic value of a $>2 \log_{10}$ IU/mL decline in HDV RNA levels, only one reported a statistically significant difference compared to having a decline of $<2 \log_{10}$ IU/mL. This study reported on 41 patients with CHD who were treated with 2 different doses of IFN or with no treatment, using the HDV RNA level at last evaluation to determine the decline

in HDV RNA from baseline¹⁷. The authors reported that the most striking finding was that patients with reduced viral loads of $>2 \log_{10}$ copies/mL had significantly improved hepatic function and liver histology.

The results from this study were the basis for an international expert panel proposing a combined response criteria for drug development studies¹⁸. This is defined as $>2 \log_{10}$ decline in HDV RNA combined with normal ALT levels as an intermediate endpoint when the desired endpoint of HDV RNA $<$ lower limit of detection (LLoD) at 48 weeks cannot be achieved. However, two more recent studies have since failed to find an association between $>2 \log_{10}$ IU/mL decline in HDV RNA and improved clinical outcomes (Table 5).

Summary of prognostic evidence

Overall, the commentary noted that the evidence is supportive of a clinical benefit for CHB/CHD patients who are either HDV RNA negative at baseline or are HDV RNA positive and subsequently clear the HDV RNA to undetectable levels as they are less likely to develop liver-related adverse events such as hepatic decompensation, HCC, liver transplantation or death. Some evidence suggested that patients with lower detectable viral loads may have a reduced risk of developing liver-related clinical events compared to those with higher detectable viral loads. However, the commentary concluded that there was no clear evidence to support a reduction of viral load by $>2 \log_{10}$ IU/mL conferring any clinical benefits, as the absolute viral load reached is also important. In fact, a review identified by the resubmission¹⁹ raised the point that the clinical benefit could differ in patients with very high baseline HDV RNA achieving a 2- \log_{10} decline to 10^4 – 10^5 IU/mL versus patients whose 2- \log_{10} decline achieves levels of 10^2 IU/mL or lower. Interestingly, two studies reported that those who responded to antiviral treatments and cleared the infection had lower HDV RNA levels at baseline than those who did not respond to treatment²⁰.

Taken together, the commentary concluded that the data suggest that a qualitative result (detectable vs undetectable) could be sufficient to provide the clinician with the information required for the likely progression of disease and to guide patient management. There is insufficient evidence to support the premise that reporting quantitative HDV RNA levels provides additional prognostic information to the clinician or the patient.

The commentary noted that this contrasts with the claim by the resubmission that “the studies, both old and new, consistently demonstrate that substantially higher viral loads are associated with worse liver outcomes,” and “further validating HDV RNA quantification as a predictor of disease progression.”

¹⁷ Farci, P, Roskams, T, Chessa, L, Peddis, G, Mazzoleni, AP, Scioscia, R, Serra, G, Lai, ME, Loy, M, Caruso, L, Desmet, V, Purcell, RH and Balestrieri, A 2004, 'Long-term benefit of interferon alpha therapy of chronic hepatitis D: regression of advanced hepatic fibrosis', *Gastroenterology*, vol. 126, no. 7, pp. 1740-1749.

¹⁸ Yurdaydin, C, Keskin, O, Kalkan, C, Karakaya, F, Caliskan, A, Kabacam, G, Onder, FO, Karatayli, S, Karatayli, E, Deda, X, Bozkaya, H, Bozdayi, AM and Idilman, R 2018, 'Interferon Treatment Duration in Patients With Chronic Delta Hepatitis and its Effect on the Natural Course of the Disease', *J Infect Dis*, vol. 217, no. 8, pp. 1184-1192.

¹⁹ Ghany, MG, Buti, M, Lampertico, P and Lee, HM 2023, 'Guidance on treatment endpoints and study design for clinical trials aiming to achieve cure in chronic hepatitis B and D: Report from the 2022 AASLD-EASL HBV-HDV Treatment Endpoints Conference', *Hepatology*, vol. 78, no. 5, pp. 1654-1673.

²⁰ Roulot, D, Brichler, S, Layese, R, BenAbdesselam, Z, Zoulim, F, Thibault, V, Scholtes, C, Roche, B, Castelnau, C, Poynard, T, Chazouillères, O, Ganne, N, Fontaine, H, Gournay, J, Guyader, D, Le Gal, F, Nahon, P, Roudot-Thoraval, F and Gordien, E 2020, 'Origin, HDV genotype and persistent viremia determine outcome and treatment response in patients with chronic hepatitis delta', *J Hepatol*, vol. 73, no. 5, pp. 1046-1062.

Wranke, A, Hardtke, S, Heidrich, B, Dalekos, G, Yalçin, K, Tabak, F, Gürel, S, Çakaloğlu, Y, Akarca, US, Lammert, F, Häussinger, D, Müller, T, Wöbse, M, Manns, MP, Idilman, R, Cornberg, M, Wedemeyer, H and Yurdaydin, C 2020, 'Ten-year follow-up of a randomized controlled clinical trial in chronic hepatitis delta', *J Viral Hepat*, vol. 27, no. 12, pp. 1359-1368.

Predictive evidence

Both the previous submission and the resubmission did not identify any studies reporting on the ability of HDV RNA testing, using either qualitative or quantitative reporting, to predict response to bulevirtide treatment.

Five studies provided evidence that quantification of HDV RNA levels at baseline and/or during antiviral treatment, mostly with conventional or pegylated IFN, predicted response to treatment and/or the likelihood of having a relapse.

The three studies assessing the ability of HDV RNA levels to predict response to anti-viral treatments reported that HDV RNA levels significantly decreased during the earlier months of treatment in patients who cleared the HDV RNA to undetectable levels.

In contrast, the three studies reporting on the ability of HDV RNA levels to predict relapse in patients who had responded to treatment and cleared the HDV infection, such that HDV RNA levels were undetectable, had inconsistent findings.

Overall, the evidence suggests that early treatment response, as measured by HDV RNA levels measured at regular intervals during treatment can predict the longer-term outcomes of treatments such as IFN. The commentary noted that the ability of HDV RNA levels to predict relapse is inconsistent, suggesting that relapse may not be predictable based on HDV RNA levels alone. Additionally, the commentary noted that it is also uncertain if the same HDV RNA dynamic response would be associated with clearance of HDV RNA after treatment with bulevirtide, as none of the studies used this treatment. However refer to the discussion below of an additional study that was identified post-ESC.

Change in management in practice

The Commentary on the previous submission found two studies that reported on the use of HDV RNA test results to alter the management of patients treated with bulevirtide.

The updated searches, conducted by the resubmission identified four articles reporting on a change in management after the monitoring of HDV RNA levels. These four articles represent only two bodies of work. One was a review (report of a conference) that was published in two different journals. The other was a clinical study that was published as a conference poster and as a peer-reviewed article presenting overlapping data. *Only the clinical study was included as new evidence in the analysis of the change in management evidence presented by the resubmission.*

The study identified by the resubmission found that a more sensitive HDV RNA PCR test (with a lower LLoD than the in-house PCR test routinely used by the German laboratory) was able to detect relapse in 3/6 patients earlier than the in-house test used for routine monitoring, but it is unclear if this would have affected the decision to retreat the patient or not²¹. However, it does illustrate the importance of using a test with a low LLoD when using undetectable HDV RNA as an endpoint for clinical management.

Limited evidence was identified in the previous Commentary linking HDV RNA monitoring to changes in management. One uncontrolled before-and-after study of 15 patients from Austria reported that 2/15 patients had their bulevirtide treatment stopped due to a maintained virological response (>6 months), and that one patient had their treatment regimen altered (by the addition of pegylated IFN) due to a lack of virological response to bulevirtide²². Another

²¹ Anastasiou, OE, Caruntu, FA, Curescu, MG, Yalcin, K, Akarca, US, Gürel, S, Zeuzem, S, Erhardt, A, Lüth, S, Papatheodoridis, GV, Keskin, O, Port, K, Radu, M, Celen, MK, Idilman, R, Heidrich, B, Mederacke, I, von der Leyen, H, Kahlhöfer, J, von Karpowitz, M, Hardtke, S, Cornberg, M, Yurdaydin, C and Wedemeyer, H 2024, 'Five-year follow-up of 96 weeks peginterferon plus tenofovir disoproxil fumarate in hepatitis D', *Liver International*, vol. 44, no. 1, pp. 139-147.

²² Binter T, Jachs M, Hartl L, Aberle S, Zoller H, Aigner E. Efficacy of long-term treatment of chronic hepatitis D patients with bulevirtide - results of a "real world" study. *Hepatology*. 2021;74:420A-1A.

patient with a maintained virological response - the planned endpoint for stopping treatment - did not have their treatment stopped. However this study was an abstract with incomplete results of a later study with updated results discussed below which did provide more evidence of change in management (see 'Critical appraisal of Jachs et al'). A case series of 114 patients treated with bulevirtide in Germany reported that one patient ceased treatment due to lack of response (likely determined by HDV RNA, although it was not explicitly described how this was defined)²³.

Some of the remaining studies included in the previous submission and mentioned in the resubmission were considered in the previous evaluation and found that monitoring of HDV RNA levels during treatment (mostly with pegylated IFN) could predict response to treatment and/or relapse and hypothesised ways in which HDV RNA testing could potentially be used to alter the management of patients receiving pegylated IFN. These studies showed HDV RNA levels could potentially affect patient management by:

- establishing stopping rules²⁴,
- individualising treatment (continuing treatment or reinstating treatment depending on response)²⁵
- motivating patients who are found to have virological response to treatment to continue with treatment, despite side effects²⁶.

In contrast to these findings, another study found no predictive evidence and concluded that it would be very difficult to use on-treatment monitoring of HDV RNA levels to develop stopping rules or even to individualize treatment duration²⁷.

Overall, the commentary concluded that these results indicate that few patients have had a change in management due to monitoring of HDV RNA levels during any anti-viral treatment. It is therefore unclear how 6-monthly HDV RNA PCR test results would be used to influence ongoing management of patients with CHD receiving bulevirtide in the absence of guidelines and evolving literature. Thus, the commentary concluded that it is possible that quantitative HDV RNA test results will have little direct clinical utility in Australia, at this time.

²³ Dietz-Fricke C, Tacke F, Zollner C, Demir M, Schmidt HH, Schramm C, et al. Treating hepatitis D with bulevirtide - Real-world experience from 114 patients. *JHEP Rep.* 2023 Apr;5(4):100686.

²⁴ Erhardt, A, Gerlich, W, Starke, C, Wend, U, Donner, A, Sagir, A, Heintges, T and Haussinger, D 2006, 'Treatment of chronic hepatitis delta with pegylated interferon-alpha2b', *Liver Int*, vol. 26, no. 7, pp. 805-810.

²⁵ Erhardt, A, Gerlich, W, Starke, C, Wend, U, Donner, A, Sagir, A, Heintges, T and Haussinger, D 2006, 'Treatment of chronic hepatitis delta with pegylated interferon-alpha2b', *Liver Int*, vol. 26, no. 7, pp. 805-810.

Castelnau, C, Le Gal, F, Ripault, MP, Gordien, E, Martinot-Peignoux, M, Boyer, N, Pham, BN, Maylin, S, Bedossa, P, Deny, P, Marcellin, P and Gault, E 2006, 'Efficacy of peginterferon alpha-2b in chronic hepatitis delta: relevance of quantitative RT-PCR for follow-up', *Hepatology*, vol. 44, no. 3, pp. 728-735.

Manesis, EK, Schina, M, Le Gal, F, Agelopoulou, O, Papaioannou, C, Kalligero, C, Arseniou, V, Manolakoulou, S, Hadziyannis, ES, Gault, E, Koskinas, J, Papatheodoridis, GV and Archimandritis, AJ 2007, 'Quantitative analysis of hepatitis D virus RNA and hepatitis B surface antigen serum levels in chronic delta hepatitis improves treatment monitoring', *Antiviral Therapy*, vol. 12, no. 3, pp. 381-388.

²⁶ Manesis, EK, Schina, M, Le Gal, F, Agelopoulou, O, Papaioannou, C, Kalligero, C, Arseniou, V, Manolakoulou, S, Hadziyannis, ES, Gault, E, Koskinas, J, Papatheodoridis, GV and Archimandritis, AJ 2007, 'Quantitative analysis of hepatitis D virus RNA and hepatitis B surface antigen serum levels in chronic delta hepatitis improves treatment monitoring', *Antiviral Therapy*, vol. 12, no. 3, pp. 381-388.

²⁷ Heidrich, B, Yurdaydin, C, Kabacam, G, Ratsch, BA, Zachou, K, Bremer, B, Dalekos, GN, Erhardt, A, Tabak, F, Yalcin, K, Gurel, S, Zeuzem, S, Cornberg, M, Bock, CT, Manns, MP, Wedemeyer, H and Group, H-S 2014, 'Late HDV RNA relapse after peginterferon alpha-based therapy of chronic hepatitis delta', *Hepatology*, vol. 60, no. 1, pp. 87-97.

Critical appraisal of Jachs et al

Post-ESC a critical appraisal of Jachs et al was requested. This is provided below.

In the study, two different tests were used at the various sites:

- Vienna, Linz and Salzburg HDV-RNA was quantified by PCR with LLoD = 100 copies/ml
- Innsbruck and the Hall group used the RoboGene® assay with LLoD = 6 IU/ml x37 = 222 copies/ml

23 patients received BLV:

- 22 patients received 2 mg/day BLV, the dose was increased from 2 mg to 10 mg/day for 1 patient
- 1 patient received 10 mg/day BLV
- Responders defined as >2 log reduction or undetectable HDV RNA
- 1 patient did not show up after week 8 (*and was excluded from the analysis*).

Previous/additional treatments:

- 18 were previous PEG-IFN non-responders
- 21 were on concomitant nucleos(t)ide analogues (ETV:3, TDF:16, TAF:2)
- 22 patients completed at least 24 (24-137) weeks of BLV

Table 8 provides a summary of responders and non-responders to BLV treatment for at least 24 weeks.

Table 6 Responders and non-responders to BLV treatment for at least 24 weeks

Week 24	Week 36	Week 48	Week 60
10/22 responders 7/10 had normal ALT	11/20 responders 10/11 had normal ALT	13/20 responders 12/13 had normal ALT	9/13 responders 8/9 normal ALT
12/22 non-responders 7/12 had normal ALT	9/20 non-responders 7/9 had normal ALT	7/20 non-responders 6/7 had normal ALT	4/13 non-responders 4/4 had normal ALT

The smaller tables below provide a summary of patients subject to a change in management.

Week 24	Week 36	Week 48	Week 60
1 responder had liver transplant at week 25 for HCC (preplanned - received BLV treatment until a donor organ became available) (<i>as it was preplanned, the transplant was not guided by the HDV RNA result</i>)			
-2.1 log HDV-RNA + normal ALT			Undetectable HDV RNA

2 responders stopped treatment at week 48 after having undetectable HDV RNA for <24 weeks (<i>both relapsed</i>)			
1 had undetectable HDV RNA + normal ALT 1 had -1.36 log HDV RNA + elevated ALT	Both undetectable HDV RNA Normal ALT	Both undetectable HDV RNA Normal ALT	HDV RNA was detectable (level NR) in both but normal ALT

1 responder stopped treatment at week 63 after having undetectable HDV RNA for <24 weeks (<i>relapsed 4 weeks later</i>)			
-1.14 log HDV RNA + elevated ALT	-1.56 log HDV RNA + normal ALT	Undetectable HDV RNA Normal ALT	HDV RNA detectable at week 67 and resumed treatment

2 responders and 1 non-responder at week 36 received PEG-IFN in addition to BLV before week 48 (<i>PEG-IFN achieved a response in non-responder</i>)			
1. -2.6 log HDV RNA 2. -2.15 log HDV RNA 3. -0.86 log HDV RNA All had normal ALT	1. -2.59 log HDV RNA 2. -2.39 log HDV RNA 3. -1.75 log HDV RNA All had normal ALT	1. -3.0 log HDV RNA 2. -3.0 log HDV RNA 3. -2.71 log HDV RNA All had normal ALT	1. -2.90 log HDV RNA 2. -3.0 log HDV RNA 3. NR Both had normal ALT

1 non-responder had cirrhosis with marked portal hypertension (HVPG 18 mm Hg, thrombo- and leucopenia) received 2 mg/day BLV which increased to 10 mg/day after 24 weeks. PEG-IFN was added at week 58 together with 25 mg Eltrombopag QD and 48 MU/week filgrastim, leading to a rapid decline of HDV-RNA (<i>assuming this occurred after week 60, as data was not captured in Table 2</i>)			
1. -0.68 log HDV RNA, elevated ALT	1. -0.72 log HDV RNA, elevated ALT	1. -1.16 log HDV RNA, elevated ALT	1. -1.20 log HDV RNA, normal ALT

2 non-responders at week 36 received PEG-IFN in addition to BLV before week 60 (<i>both had an improved response</i>)			
1. -0.5 log HDV RNA, normal ALT 2. -1.29 log HDV RNA, elevated ALT	1. -0.46 log HDV RNA, normal ALT 2. -1.69 log HDV RNA, elevated ALT	1. -0.47 log HDV RNA, normal ALT 2. -1.32 log HDV RNA, normal ALT	1. -2.31 log HDV RNA, normal ALT 2. -1.90 log HDV RNA, normal ALT

1 non-responder had treatment stopped because of severe alcohol abuse. Treatment was restarted after 6 months of sobriety and PEG-IFN was added after 20 weeks			
-1.32 log HDV RNA, elevated ALT	NR	NR	NR

1 responder received PEG-IFN in addition to BLV before week 60 and then had treatment terminated because of intolerability of the combination PEG-IFN with BLV at week 60			
-0.74 log HDV RNA, normal ALT	NR, normal ALT	-1.67 log HDV RNA, normal ALT	-2.30 log HDV RNA, elevated ALT

All 5 patients who stopped treatment at weeks 48-130, after having undetectable HDV RNA for at least 6 months, relapsed.

10 patients were still on BLV monotherapy at the end of the study, but details on HDV RNA and ALT levels were only shown for 7 of these patients. Five were responders and 2 had not responded to BLV treatment (with 0.82 and 1.25 log decreases in viral load). The reasons why PEG-IFN was not added to the treatment of these patients was not discussed.

The addition of PEG-IFN resulted in a >2 log decrease in HDV RNA in 3 out of 6 non-responders to BLV monotherapy. No explanation was given as to why the other non-responders were not given PEG-IFN, though it may be related to the finding of a normal ALT. The log decrease in viral load did not in isolation appear to factor into the decision about which non-responders should have PEG-IFN treatment in addition to BLV. As only the change in HDV RNA levels has been reported, it is unknown what the residual viral load is in these patients, i.e. whether it is low (as in close to undetectable) or high. Thus, it cannot be determined if the level of residual HDV RNA plays a role in determining clinical management.

PEG-IFN treatment was added to 2 patients who responded to BLV with a >2 log decrease due an increase in HDV-RNA at week 44 in one patient (not captured with information provided in Table 2). The other patient had a >2 log decrease at week 24, which did not decrease any further, thus PEG-IFN was thus added at week 39. The decision to change treatment for these 2 patients does appear to be directly related to the quantitative HDV RNA result, but was influenced by the trend.

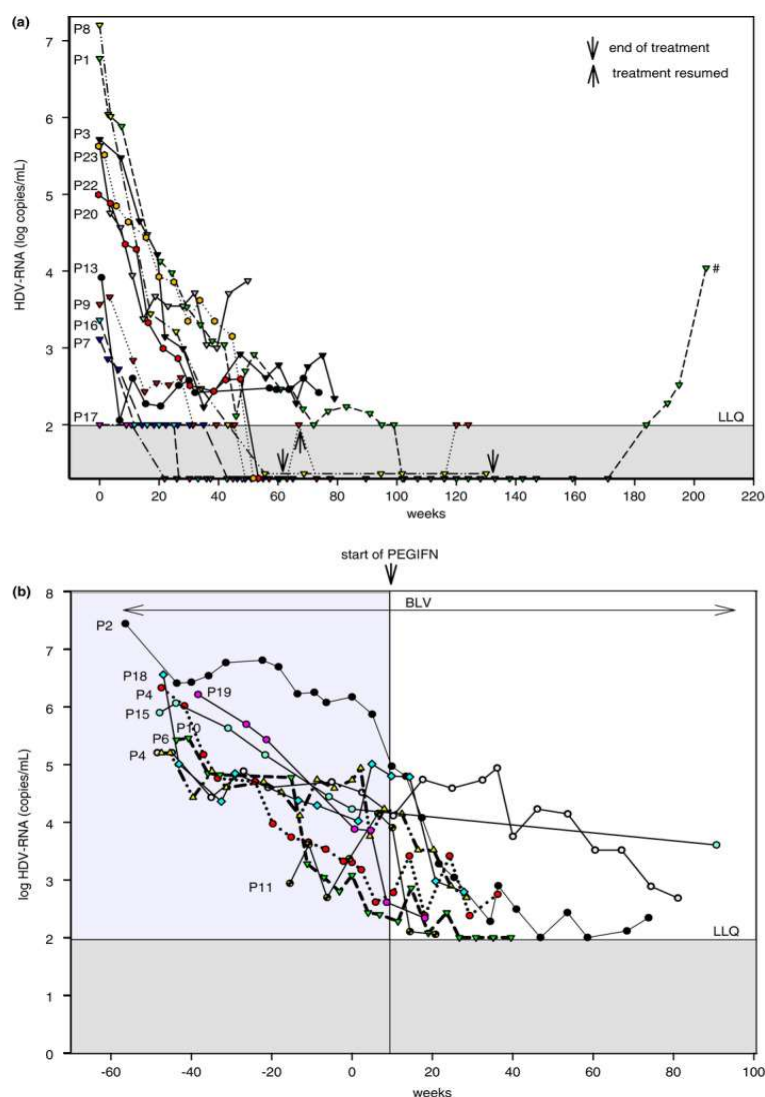


Figure 3 (A) HDV-RNA in patients on BLV monotherapy responding to BLV. Data of treatment of patient P1 until week 24 of follow-up were published. 16 # retreatment with 2 mg BLV/day is considered. **(B)** Changes in HDV-RNA before and after the addition of PEG-IFN

Discussion of the results

The authors noted that there is a lack of an accepted surrogate for virological efficacy of BLV therapy. However, the use of a combination of a >2 log decrease in viral load and normalisation of ALT as a primary endpoint implies that many patients still have detectable HDV-RNA and the impact of incomplete viral suppression on the further evolution of CHD remains unknown. Furthermore, the authors noted that ALT is an uncertain marker of liver disease and patients with advanced chronic liver disease may have ALT in the normal range. *In fact, 58%, 78%, 86% and 100% of non-responders had normal ALT levels at weeks 24, 36, 48 and 60, respectively.*

Thus, the authors performed paired hepatic venous pressure gradient (HVPG) measurements, as a 10%-decrease in HVPG translated into a decreased risk of hepatic decompensation in patients achieving HCV cure as well as favourable outcomes in studies investigating medical therapies for portal hypertension.

Paired data on liver stiffness at baseline and at 48 weeks of treatment was available in 11 patients (*six responders at 1 year and five non-responders*). Liver stiffness decreased in nine out of 11 patients and did not seem to correlate with the degree of virological response. Only two patients showed increases in liver stiffness; the patient in whom treatment was suspended due to alcohol abuse (with the increase most likely due to the alcohol abuse), and another patient who was an excellent virological responder (*-2.08 log decrease at 1 year*).

The use of PEG-IFN in the change in management for some of these patients may not be applicable to the Australian setting as PEG-IFN is not TGA-approved for this indication.

Although the decision to add PEG-IFN treatment for two patients who responded to BLV treatment seems to have been guided by the residual viral load detected, the same cannot be concluded for those patients classed as non-responders. Some non-responders received PEG-IFN and some did not. The reasons for the discrepancy in treatments were not discussed in this study.

Claim of codependence

The resubmission noted that 'The ESC for both the PBAC and MSAC considered "the claim of codependence was reasonable for HDV RNA PCR testing to establish the presence of chronic HDV infection and for access to treatment with bulevirtide"'

The commentary concluded that the claim of codependence for HDV RNA PCR testing for monitoring of response to bulevirtide was not properly addressed in the previous submission. In the PSD, MSAC considered it was unknown whether the level of HDV RNA (other than the presence of HDV RNA) would be used to alter patient management in non-responders or partial responders.

The resubmission claimed that "codependence will be met when HEPCLUDEX and the HDV RNA PCR test are both recommended and available on the PBS and MBS, respectively." The resubmission also claimed that "viral load reduction is required to be measured to ensure patient is benefitting from treatment," establishing "codependence of the test with HEPCLUDEX for both establishing the presence of chronic HDV and the monitoring of viral load for continued treatment with HEPCLUDEX."

However, the commentary noted that no patient had a change in management due to monitoring of HDV RNA levels detected by the PCR test in the key clinical trial, MYR301. Patients not responding to treatment (where HDV RNA levels did not decline sufficiently) and those with sustained undetectable HDV RNA did not stop treatment.

Additionally, the commentary noted that the literature searches in the ADAR identified scant evidence that HDV RNA levels would guide patient management. Two patients had treatment stopped due to insufficient response, and no patients had a change in management reported in the literature due to a reduction of $>2 \log_{10}$ IU/mL in viral load. Only two other patients who had a change in management following HDV RNA PCR testing were identified; in both these instances the change in management (stopping of treatment) was due to a qualitative test result showing sustained undetectable HDV RNA (i.e. below the LLoD of the test) for at least 6 months. However additional evidence was identified and discussed at ESC (refer to 'ESC discussion').

The commentary noted that it remains unclear how quantitative HDV RNA PCR testing to monitor the response to bulevirtide would influence bulevirtide use. Thus, the commentary concluded that the resubmission has not established codependency between monitoring of HDV RNA levels using the PCR test and bulevirtide treatment.

The above represents the commentary's view of the claim of codependence. However refer to 'Summary of consideration and rationale for MSAC's advice'.

13. Economic evaluation

Structure of the economic model

The resubmission presented an updated modelled economic evaluation, based on the Week 144 data from the key trial MYR301 that compared bulevirtide treatment to best supportive care (BSC) in patients with HDV RNA positive CHD. The type of economic evaluation presented was a cost-utility analysis, measuring outcome in terms of quality-adjusted life years (QALYs) gained. This is unchanged from the previous submission.

No alternative scenarios of test/treatment provision were explored in the resubmission. The previous Commentary noted that there may be some benefits of HDV RNA testing, independent of guiding treatment, given the prognostic information about a patient's HDV that RNA testing may provide. This approach was supported by public consultation received on the PICO Confirmation but was not addressed in the resubmission.

The structure of the model remains the same as in the previous submission. Patients enter the economic model at the point of treatment, and the cost of identifying one patient eligible for bulevirtide is applied as a one-off cost at Cycle 0. As in the previous submission, the resubmission's base case analysis assumed 100% sensitivity and 100% specificity for HDV RNA PCR testing. When the March 2024 submission was considered, the MSAC noted that there were numerous and important uncertainties associated with the economic model because it did not take into account false positive and false negative test results, and the pattern of use of testing and retesting (p2 and p7, Application No. 1708 PSD, April 2024 MSAC meeting). The resubmission argued that the clinical evidence showed high performance accuracy for HDV RNA testing and the change in LLoD is unlikely to change the diagnostic accuracy. Therefore, false positives and false negatives were not modelled in the base case. To address MSAC concern regarding the impact of false negative and false positive results from HDV RNA testing at initial diagnosis, the resubmission presented a scenario analysis comparing bulevirtide with BSC, by assuming 95% sensitivity and 95% specificity for the HDV RNA PCR test. Refer to the "Scenario analysis" subsection below. Based on the clinical evidence that the qualitative (positive/negative) concordance of the VIDRL in-house test compared with the RoboGene clinical utility standard was **redacted** positive percent agreement and **redacted** negative percent agreement, an additional analysis was performed by assuming **redacted** sensitivity and **redacted** specificity.

In the base case analysis, the HDV RNA positivity rate in anti-HDV positive patients was estimated based on the same studies as in the previous submission (Coghill et al. (2018), Jackson et al. (2018) and Shadur et al. (2013))²⁸, with the weighted average corrected to 54.4% (vs. 56.2% in the previous submission) as per the March 2024 Commentary. By assuming 100% sensitivity and 100% specificity, it was estimated that 1.84 patients (=1/54.4%) would require testing to identify one patient eligible for treatment.

The resubmission assumed 6-monthly HDV RNA testing while patients remain on treatment. While this is consistent with the proposed MBS item, the only change in management modelled due to the inclusion of HDV RNA monitoring is to cease treatment in non-responders at Week 144. Patients who respond to treatment were assumed to remain on bulevirtide unless they experience disease progression, HBsAg seroclearance, or discontinue due to other reasons. The role of testing to monitor HDV RNA levels during bulevirtide treatment is highly uncertain.

²⁸ Coghill S, McNamara J, et al. Epidemiology and clinical outcomes of hepatitis delta (D) virus infection in Queensland, Australia. *Int J Infect Dis*. 2018 Sep;74:123-7.

Jackson K, MacLachlan J, et al. Epidemiology and phylogenetic analysis of hepatitis D virus infection in Australia. *Intern Med J*. 2018 Nov;48(11):1308-17.

Shadur B, MacLachlan J, Cowie B. Hepatitis D virus in Victoria 2000-2009. *Intern Med J*. 2013 Oct;43(10):1081-7.

The base case analysis was generated using the same approach as per the original submission, with the following main changes in model inputs:

- The updated virological response rates up to 144 weeks in the MYR301 trial. Although the use of trial data with the longest follow-up is appropriate, the treatment response applied in the model (undetectable HDV RNA or decrease in HDV RNA levels by $\geq 2 \log_{10}$ IU/mL) is neither the primary efficacy endpoint in the key trial (undetectable HDV RNA or decrease in HDV RNA levels by $\geq 2 \log_{10}$ IU/mL from baseline and ALT normalisation) nor the surrogate measure (undetectable HDV RNA levels) used to estimate the effect of response on liver-related clinical outcomes (see the dot point below).
- The HRs for disease progression of CHD in responders sourced from a recently published meta-analysis by Gish et al. (2024)²⁹. Several studies in the meta-analysis included irrelevant comparisons, e.g. acute versus chronic HDV infections and HBV mono-infection versus HBV/HDV infection, limiting the applicability to the target clinical benefit of a response in patients with CHD. Also, Gish et al.'s meta-analysis missed one relevant study identified by the sponsor-commissioned meta-analysis presented in the previous submission³⁰. In the clinical studies where relevant comparisons were presented, the definition used for the surrogate outcome measure (detectable versus undetectable HDV RNA) was narrower than the definition of virological response used in the economic model (undetectable HDV RNA or decrease in HDV RNA levels by $\geq 2 \log_{10}$ IU/mL). The use of undetectable viral load as the response measure would be more consistent with studies used to quantify the effect of virological response on clinical outcomes.
- The extended duration of bulevirtide treatment. The resubmission assumed that all patients in the bulevirtide arm would receive 144 weeks of bulevirtide treatment, unless they experience HBsAg seroclearance, disease progression (decompensated cirrhosis (DCC) or HCC) or death. After Week 144, non-responders were assumed to cease treatment. Responders were assumed to continue treatment unless they experienced the events noted above or discontinued due to other reasons. It is unknown whether the treatment duration modelled in the economic evaluation would reflect clinical practice. The proposed PBS restriction did not specify stopping rules and/or treatment continuation criteria. The decision to continue or cease treatment, based on virological response, is likely to be a matter of clinical judgement and the available evidence suggests that changes in management are rarely exercised on the basis of changes in HDV RNA levels (see Clinical section).
- The updated utilities associated with non-cirrhosis (NC) and compensated cirrhosis (CC) health states based on Australian population weights. The utilities for the NC and CC patients applied to the resubmission's model lack face validity and are notably higher than the utility weights in the HCV model previously considered by the PBAC.

Other major areas of concern in the economic model, previously noted by the PBAC, include the assumption of a utility gain in the responders, the time horizon, the source used to model the natural history of chronic HDV, and the rate of compliance with bulevirtide treatment. These model inputs essentially remain unchanged since the previous submission and their continued use has not been adequately justified in the resubmission.

²⁹ Gish RG, Wong RJ, Di Tanna GL, et al. Association of hepatitis delta virus with liver morbidity and mortality: A systematic literature review and meta-analysis. *Hepatology* (Baltimore, Md). 2024;79(5):1129-40.

³⁰ Palom A, Sopena S, et al. One-quarter of chronic hepatitis D patients reach HDV-RNA decline or undetectability during the natural course of the disease. *Alimentary Pharmacology & Therapeutics*. 2021;54(4):462-9.

Results of the economic analysis

The proposed cost of HDV RNA PCR testing to determine a patient's eligibility for bulevirtide therapy was \$152.10 per test. Assuming that 54.4% of anti-HDV antibody positive patients would be positive for HDV RNA, the one-off cost applied on model entry to identify one patient eligible for treatment was \$279.60. HDV RNA monitoring was assumed twice per year while on treatment. Therefore, the cost per year for monitoring was \$304.20. Given that the duration of bulevirtide treatment modelled was 12.3 years, the cost of test monitoring applied per treatment course would be \$redacted (undiscounted).

The results of the stepped economic evaluation are presented in Table 7. To keep consistent with the previous Commentary, additional steps (3a and 3b) were included from Step 3 to Step 4 to allow the effect of transformations to be distinguished from one another.

Table 7 Results of the stepped economic evaluation

Step and component	Bulevirtide	BSC	Increment
Step 1: Trial-based costs and outcomes (48 weeks)			
Trial-based analysis at 48 weeks. Cost of testing to identify one patient with detectable HDV RNA included (assuming 54.4% positivity rate). Compliance with bulevirtide treatment was 99.55% based on MYR301 trial compliance at 48 weeks (equivalent to 5.57 scripts per patient per 48 weeks).			
Costs	\$ redacted	\$0	\$ redacted
Virological response ^a at 48 weeks	73.5%	3.9%	69.5%
Incremental cost/additional responder			\$ redacted
Step 2: Trial-based costs and outcomes to 144 weeks, with extrapolation of comparator outcomes			
Trial-based analysis at 144 weeks, assuming extrapolation of virological response in the comparator arm. Compliance with bulevirtide treatment was 96.75% based on MYR301 trial compliance at 144 weeks (equivalent to 16.25 scripts per patient per 144 weeks).			
Costs	\$redacted	\$0	\$redacted
Virological response ^a at 144 weeks	73.5%	4.4%	69.1%
Incremental cost/additional responder			\$redacted
Step 3: Transformation of virological response into QALYs			
A utility increment of 0.033 × 2.00 years (i.e. 144 weeks) was applied per patient with virological response at 144 weeks.			
Costs	\$redacted	\$0	\$redacted
QALY gained	0.067	0.004	0.063
Incremental cost/extra QALY gained			redacted ¹
Step 3a: Transformation of the surrogate outcome of virological response into effect on disease progression			
<i>Differences in disease progression were modelled across responders and non-responders based on the estimated relationship between virological response and liver-related outcomes. While the cost of testing was unchanged from the steps prior, the cost of bulevirtide treatment was reduced due to disease progression or HBsAg seroclearance. Costs of managing AEs, monitoring costs and other health state costs (disease management, liver transplantation and liver-related death) were included. Utility weights were applied according to the time spent in each health state and disutility due to AEs was included.</i>			
Costs	\$redacted	\$15,160	\$ redacted
LY gained	2.43	2.39	0.04
QALY gained	2.24	2.12	0.12
Incremental cost/extra QALY gained			redacted ²
Step 3b: Adjustment of compliance to bulevirtide treatment			
<i>Costs and outcomes as per Step 3a, except bulevirtide costs were adjusted for reduced compliance (90%)</i>			
Costs	\$ redacted	\$15,160	\$ redacted
LY gained	2.43	2.39	0.04
QALY gained	2.24	2.12	0.12
Incremental cost/extra QALY gained			redacted ³
Step 4: Extrapolation over 58 years			
Cost of testing and costs and outcomes due to AEs were unchanged from previous steps. All other costs and outcomes were extrapolated over 58-year time horizon.			
Costs	\$ redacted	\$71,803	\$ redacted
LY gained	11.38	8.47	2.91
QALY gained	10.06	7.11	2.95
Incremental cost/extra QALY gained (base case)			redacted ⁴

Source: Table 3.8-1, p142 of the of the resubmission.

The redacted value corresponds to the following range

1. > \$1,055,000
2. \$755,000 to <\$855,000
3. \$655,000 to <\$755,000
4. \$95,000 to <\$115,000

AE = adverse event; BSC = best supportive care; HBsAg = hepatitis B surface antigen; HDV = hepatitis D virus; LYs = life years; QALYs = quality adjusted life years; RNA = ribonucleic acid.

Note: Analyses in *italics* were conducted during the evaluation.

^a Defined as undetectable HDV RNA or decrease in HDV RNA by ≥2 log₁₀ IU/mL from baseline.

Sensitivity analyses were conducted during the evaluation to explore the sensitivity of the model to inputs related to testing. In general, the incremental cost-effectiveness ratio (ICER) is not sensitive to changes related to testing able to be explored with the provided model structure. The

results of the univariate sensitivity analyses show that the ICER is sensitive to the definition of virological response, the source used to model CHD disease progression, and the time horizon. The results are also sensitive to changes in health state utilities for NC and CC, utility increment in responders, treatment compliance, and HRs for disease progression in responders. However the ESCs noted that the ICER per QALY increased by 56% to \$135,000 to <\$155,000 if the definition of a response to treatment was undetectable HDV RNA.

Scenario analysis

The structure of the scenario analysis provided in the resubmission is presented in Figure 4 below.

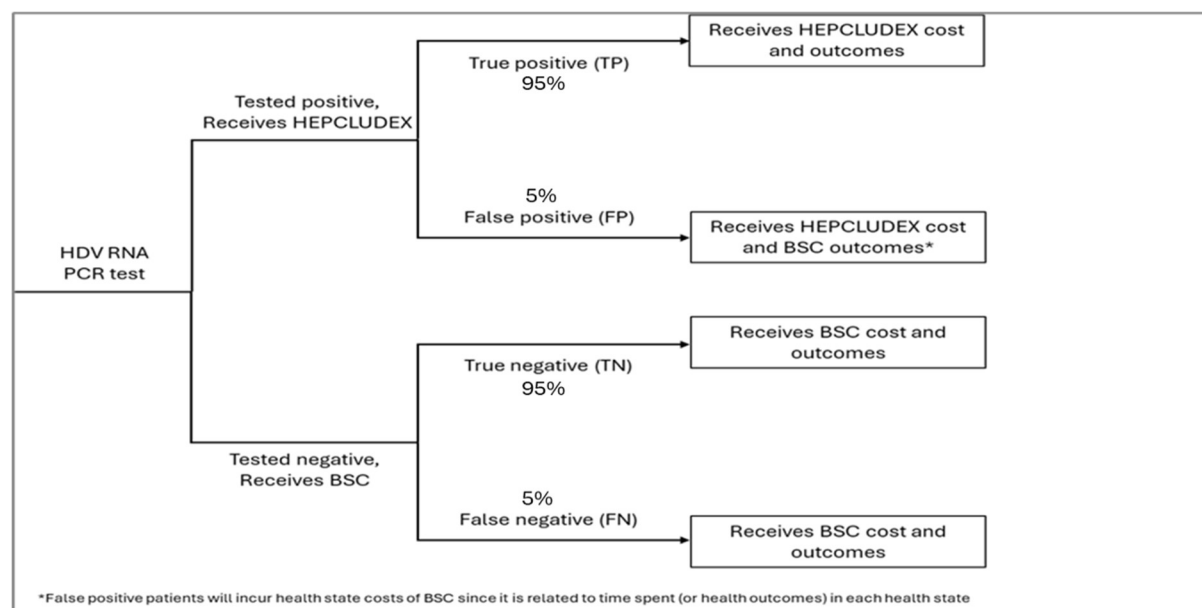


Figure 4 Model schematic – resubmission’s scenario analysis

Source: Figure 3.2-2, p109 of the resubmission.

BSC = best supportive care; HDV = hepatitis D virus; PCR = polymerase chain reaction; RNA = ribonucleic acid

The resubmission’s scenario analysis is fundamentally flawed. The scenario analysis compared use of bulevirtide in patients with CHD who tested positive, i.e. true positive (TP) (95% (=sensitivity)), plus patients without CHD who tested positive erroneously, i.e. false positive (FP) (5% (= 1-specificity)), with use of BSC in patients without CHD who tested negative, i.e. true negative (TN) (95% (= specificity)), plus patients with CHD who tested negative, i.e. false negative (FN) (5% (= 1-sensitivity)). That is, bulevirtide and BSC were not compared in the same population, but instead compared in complement subpopulations (tested positive vs. tested negative) which make up the whole tested population. In addition, the assumptions underpinning the determination of the health outcomes in patients without CHD infection (TNs and FPs) and the duration of bulevirtide treatment in patients with a FP result from HDV RNA testing are not reasonable, because the analysis assumed: 1) a shorter survival for patients without CHD than those with the disease and receiving bulevirtide treatment; and 2) patients with a FP result at diagnosis of CHD would discontinue bulevirtide therapy at Week 144.

A revised analysis was performed during the evaluation which assumed all patients entering the model at the point of testing and compared two scenarios: 1) the proposed scenario where all patients undergo HDV RNA testing and are treated with bulevirtide if tested positive or with BSC if tested negative, and 2) the current scenario where the testing is not available and all patients receive BSC.

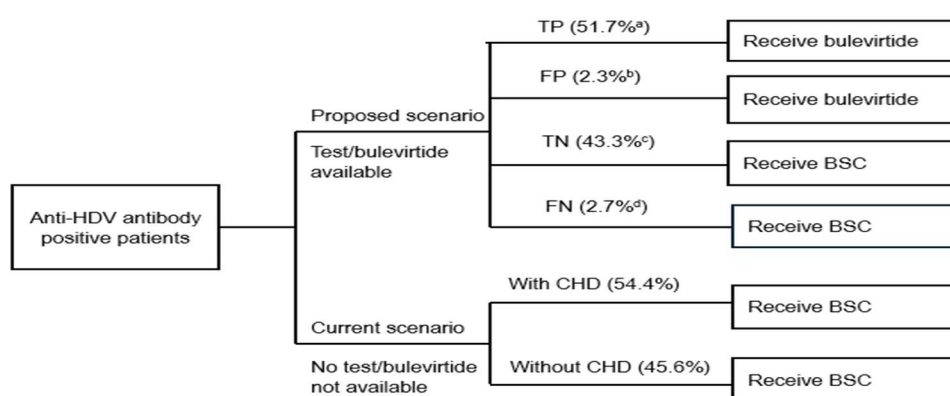


Figure 5 Model schematic – Revised scenario analysis

Source: Figure constructed during the evaluation

BSC = best supportive care; CHD = chronic hepatitis D; FN = false negative; FP = false positive; HDV = hepatitis D virus; TN = true negative; TP = true positive

^a = sensitivity x prevalence of HDV RNA positive, where sensitivity = 95% and prevalence of HDV RNA positive = 54.4%

^b = (1 - specificity) x (1 - prevalence of HDV RNA positive), where specificity = 95% and prevalence of HDV RNA positive = 54.4%

^c = specificity x (1 - prevalence of HDV RNA positive), where specificity = 95% and prevalence of HDV RNA positive = 54.4%

^d = (1 - sensitivity) x prevalence of HDV RNA positive, where sensitivity = 95% and prevalence of HDV RNA positive = 54.4%

Table 10 summarises the assumptions used to determine the costs and outcomes in each subpopulation.

Table 10 Assumptions in the revised scenario analysis

Scenario	Branch	Proportion	Assumptions
Proposed	TP	51.7%	<ul style="list-style-type: none"> - Treated with bulevirtide - Costs and outcomes assumed the same as the bulevirtide arm of the base case^a
	FP	2.3%	<ul style="list-style-type: none"> - Treated with bulevirtide - Natural disease progression of HBV mono-infection as reported in Bermingham et al. 2015 - 100% virological response (utilities for NC and CC as in responders) - No change in HBV disease progression in “responders”
	TN	43.3%	<ul style="list-style-type: none"> - Treated with BSC - Natural disease progression of HBV mono-infection as reported in Bermingham et al. 2015 - 100% virological response (utilities for NC and CC as in responders) - No change in HBV disease progression in “responders”
	FN	2.7%	<ul style="list-style-type: none"> - Treated with BSC - Costs and outcomes assumed the same as the BSC arm of the base case
Current	With CHD	54.4%	<ul style="list-style-type: none"> - Treated with BSC - Costs and outcomes assumed the same as the BSC arm of the base case
	Without CHD	45.6%	<ul style="list-style-type: none"> - Treated with BSC - Natural disease progression of HBV mono-infection as reported in Bermingham et al. 2015 - 100% virological response (utilities for NC and CC as in responders) - No change in HBV disease progression in “responders”

Source: Table compiled during the evaluation

BSC = best supportive care; CC = compensated cirrhosis; CHD = chronic hepatitis D; FN = false negative; FP = false positive; HBV = hepatitis B virus; NC = non-cirrhosis; TN = true negative; TP = true positive

^a Excluding the testing cost to identify 1 patient eligible for bulevirtide (\$279.60) in the base case. Instead, the cost per test (\$152.10) would be added to 100% of patients in the proposed scenario.

Results of the revised scenario analysis are presented in Table 8. The ICER associated with HDV RNA testing plus bulevirtide in the tested population was estimated to be \$95,000 to

<\$115,000/QALY gained using an assumed sensitivity and specificity of 95%, compared with an ICER of \$95,000 to <\$115,000/QALY gained in the treated population assuming 100% test accuracy.

Table 8 Revised scenario analysis performed during the evaluation

Scenario	Branch	Proportion	Cost	LYs	QALYs
Proposed (Testing + bulevirtide)	TP	51.7%	\$redacted	11.379	10.061
	FP	2.3%	\$redacted	11.565	10.265
	TN	43.3%	\$redacted	11.565	10.260
	FN	2.7%	\$redacted	8.466	7.109
	Total	100.0%	\$redacted^a	11.385	10.072
Current (No testing + BSC)	With CHD	54.4%	\$redacted	8.466	7.109
	Without CHD	45.6%	\$redacted	11.565	10.260
	Total	100.0%	\$redacted	9.879	8.546
Difference			\$redacted	1.505	1.526
ICER				redacted/LY	redacted¹ /QALY

The redacted value corresponds to the following range

1. \$95,000 to <\$115,000

Source: Analysis performed during the evaluation

BSC = best supportive care; CHD = chronic hepatitis D; FN = false negative; FP = false positive; ICER = incremental cost-effectiveness analysis; LYs = life years; QALYs = quality-adjusted life years; TN = true negative; TP = true positive

^a Excluding the testing cost to identify 1 patient eligible for bulevirtide (\$279.60) in the base case. Instead, the cost per test (\$152.10) would be added to 100% of patients in the proposed scenario.

Based on the clinical evidence, an additional analysis was conducted by assuming 95% sensitivity and 100% specificity. The resulting ICER is identical to the base case ICER, i.e. \$95,000 to <\$115,000/QALY gained. This is because the costs and health outcomes associated with FN results (5%) have cancelled out between the two scenarios.

14. Financial/budgetary impacts

The resubmission uses an epidemiological approach to estimate the use and cost of HDV RNA testing and bulevirtide treatment.

Use and cost of HDV RNA testing

The resubmission estimated the use and cost of HDV RNA testing for determining access to bulevirtide treatment and for monitoring while on treatment. The derivation of the HDV RNA testing population was integrated into the definition of the treated patient population. *This produced a consistent approach to the derivation of both the tested and treated populations.*

The resubmission estimated the patients eligible for HDV RNA testing and bulevirtide treatment across four population groups:

- Prevalent chronic HBV patients, who are engaged in care, with known chronic HDV (prevalent population A).
- Prevalent chronic HBV patients, who are engaged in care, but previously untested for HDV (prevalent population B).
- Prevalent chronic HBV patients, who are not engaged in care, but previously diagnosed for HDV (*not considered in the March 2024 submission*) (prevalent population C).
- Incident patients.

The resubmission retained the structure of prevalent populations A and B from the March 2024 submission, with updated parameters.

Prevalent population C is newly included in the resubmission to address the identified shortfall in the March 2024 submission. This population accounts for prevalent, but untreated chronic HBV patients who may reengage with treatment now that another treatment is available. The resubmission expects these patients to be HDV RNA tested and reengage with treatment over the first six years of the listing. This addresses the issue of lack of comprehensive population coverage that was identified in the March 2024 submission.

The details of the derivation of the three prevalent populations, applying updated parameters as given in Table 9.

Table 9 Cost of HDV RNA testing of incident and prevalent patient to determine eligibility for bulevirtide

	Parameters	Year 1 2025	Year 2 2026	Year 3 2027	Year 4 2028	Year 5 2029	Year 6 2030
Current CHB prevalent patients that have not yet been tested (Prevalent Population B) that will be tested over 3 years, 2025-2027 (Years 1-3)							
A	No. prevalent chronic HBV patients who are engaged in care prior to listing	redacted ¹					
B	Proportion of prevalent chronic HBV patients tested for anti-HDV following listing	redacted %	redacted %	redacted %			
C	CHB patients tested for HDV antibodies population	redacted ²	redacted ³	redacted ⁴			
D	No. eligible for HDV RNA testing (anti-HDV+) (C × 4.06%)	redacted ⁴	redacted ⁵	redacted ⁵			
E	Uptake of HDV RNA testing following listing	redacted%	redacted%	redacted%			
F	Patients tested for HDV RNA following listing (D × E)	redacted ⁵	redacted ⁵	redacted ⁵			

	Parameters	Year 1 2025	Year 2 2026	Year 3 2027	Year 4 2028	Year 5 2029	Year 6 2030
Current CHB diagnosed prevalent patients not engaged in care who subsequently engage in care over the period of the model (Prevalent Population C)							
G	Patients who are diagnosed and initially not engaged in care who subsequently engage in care (row P)		redacted ⁴	redacted ⁴	redacted ⁴	redacted ⁴	redacted ⁴
H	CHB patients tested for HDV antibodies		redacted %	redacted %	redacted %	redacted %	redacted %
I	No. patients tested for anti-HDV antibodies		redacted ⁴	redacted ⁴	redacted ⁴	redacted ⁴	redacted ⁴
J	No. eligible for HDV RNA testing (anti-HDV+) ($I \times 4.21\%$)		redacted ⁵	redacted ⁵	redacted ⁵	redacted ⁵	redacted ⁵
K	Uptake of HDV RNA testing following listing		redacted %	redacted %	redacted %	redacted %	redacted %
L	Patients tested for HDV RNA following listing ($J \times K$)		redacted ⁵	redacted ⁵	redacted ⁵	redacted ⁵	redacted ⁵
Incident patients							
M	CHB patients diagnosed population (row X)	redacted ³	redacted ³	redacted ³	redacted ³	redacted ³	redacted ³
Prior to listing							
N	No. chronic HBV patients tested for anti-HDV ($M \times 35.0\%$)	redacted ⁴	redacted ⁴	redacted ⁴	redacted ⁴	redacted ⁴	redacted ⁴
O	No. chronic HBV patients found with anti-HDV+ ($N \times 4.06\%$)	redacted ⁵	redacted ⁵	redacted ⁵	redacted ⁵	redacted ⁵	redacted ⁵
P	No. patients with anti-HDV+ who received HDV RNA testing ($O \times 44.4\%$)	redacted ⁵	redacted ⁵	redacted ⁵	redacted ⁵	redacted ⁵	redacted ⁵

	Parameters	Year 1 2025	Year 2 2026	Year 3 2027	Year 4 2028	Year 5 2029	Year 6 2030
After listing							
Q	Proportion chronic HBV patients tested for anti-HD	redacted %	redacted %	redacted %	redacted %	redacted %	redacted %
R	No. chronic HBV patients tested for anti-HDV (M × R)	redacted ⁴	redacted ⁴	redacted ⁴	redacted ⁴	redacted ⁴	redacted ⁴
S	No. incident chronic HBV patients found with anti-HDV+ (R × 4.06%)	redacted ⁵	redacted ⁵	redacted ⁵	redacted ⁵	redacted ⁵	redacted ⁵
T	Uptake of HDV RNA testing following listing	redacted %	redacted %	redacted %	redacted %	redacted %	redacted %
U	No. incident chronic HBV patients with anti-HDV+ who received HDV RNA testing (S × T)	redacted ⁵	redacted ⁵	redacted ⁵	redacted ⁵	redacted ⁵	redacted ⁵
V	Increase in incident patients tested with HDV RNA (U– P)	redacted ⁵	redacted ⁵	redacted ⁵	redacted ⁵	redacted ⁵	redacted ⁵
W	Total increase in patients tested for HDV RNA (F + L + V)	redacted ⁴	redacted ⁵	redacted ⁵	redacted ⁵	redacted ⁵	redacted ⁵
X	Cost to the MBS (\$129.30 per test)	redacted ⁶	\$ redacted ⁶	\$ redacted ⁶	\$ redacted ⁶	\$ redacted ⁶	\$ redacted ⁶

Source: Table 4.6-4, pp176-177 of the resubmission

CHB = Chronic Hepatitis B; HBV = Hepatitis B Virus; HDV = Hepatitis D Virus; MBS = Medicare Benefits Schedule; PCR = Polymerase Chain Reaction; RNA = Ribonucleic Acid

The redacted values correspond to the following ranges

1 50,000 to <60,000

2 10,000 to <20,000

3 5,000 to <10,000

4 500 to <5,000

5 <500

6 \$0 to < \$10 million

Use and cost of HDV RNA testing for monitoring during bulevirtide treatment

The resubmission used the treated patient population derived from the prevalent and incident patient populations to determine the number of HDV RNA tests required for monitoring. It was assumed that each patient would receive one test every six months to determine their viral load and hence suitability to continue treatment. This addresses the issue identified in the March 2024 submission that overstated the number of patients on treatment and hence the number of monitoring tests required.

Table 10 Cost of HDV RNA testing of treated patients for monitoring during bulevirtide treatment

	Parameters	Year 1 2025	Year 2 2026	Year 3 2027	Year 4 2028	Year 5 2029	Year 6 2030
A	No. patient years on treatment (row AK)	redacted ¹	redacted ¹	redacted ¹	redacted ¹	redacted ¹	redacted ²
B	No. HDV RNA monitoring tests (A x 2 per patient-year on treatment)	redacted ¹	redacted ²	redacted ²	redacted ²	redacted ²	redacted ²
C	Cost to the MBS (\$129.30 per test)	redacted ³	redacted ³	redacted ³	redacted ³	redacted ³	redacted ³

Source: Table 4.6-5, p177 of the resubmission

HDV = Hepatitis delta virus; MBS = Medicare Benefits Schedule

The redacted values correspond to the following ranges

1 <500

2 500 to <5,000

3 \$0 to < \$10 million

Table 11 Total cost of HDV RNA testing

	Parameters	Year 1 2025	Year 2 2026	Year 3 2027	Year 4 2028	Year 5 2029	Year 6 2030
A	Total cost HDV RNA PCR tests for diagnosis (Table 1 row X)	redacted ¹	redacted ¹	redacted ¹	redacted ¹	redacted ¹	redacted ¹
B	Total cost HDV RNA PCR tests for monitoring (Table 1 row C)	redacted ¹	redacted ¹	redacted ¹	redacted ¹	redacted ¹	redacted ¹
C	Total additional cost MBS (A + B)	redacted ¹	redacted ¹	redacted ¹	redacted ¹	redacted ¹	redacted ¹

The redacted values correspond to the following ranges

1 \$0 to < \$10 million

15. Other relevant information

Nil.

16. Key issues from ESC to MSAC

Main issues for MSAC consideration

Clinical issues

- *The ESCs advised that as CHD is rare and the monitoring of HDV viral load and subsequent clinical management requires more highly specialised knowledge, the ordering of monitoring tests should be limited to specialists. Restricting the ordering of monitoring tests to specialists would also make it more likely that sequential monitoring testing of the same patients would occur in the same laboratory, and thus reduce inter-laboratory variability in testing, if more laboratories were to take up this testing in the future. Therefore the ESCs recommended that MSAC consider a single MBS item to cover testing for both eligibility and monitoring which is restricted to specialists.*
- *The commentary considered that reliability of different tests in detecting similar viral loads (quantitative concordance) is problematic. Differences can be larger than 2 log₁₀ IU/mL. Three studies found that the quantitative differences between tests were large enough that they could potentially result in inappropriate changes in patient management. However the ESCs noted that currently only one laboratory in Australia, the Victorian Infectious Diseases Reference Laboratory (VIDRL), offers HDV RNA testing, thus eliminating the potential for inter-laboratory variability in results. The ESCs considered that if other laboratories were to offer HDV testing in the future, an external quality assurance program (QAP) would need to be established to ensure inter-laboratory consistency in testing. Under the Requirements for Medical Pathology Services, laboratories must be enrolled, participate and perform to an acceptable standard in external quality programs where they are available. Where such a program does not exist for a particular test method, the validity of the test results must be demonstrated by methods such as inter-laboratory comparisons or the analysis of reference material.*

Economic issues

- *The issues previously raised by the ESCs regarding the economic model remain largely unaddressed, and the model remains mostly unchanged.*
- *The economic model assumed that patients would undergo HDV RNA testing every 6 months while on bulevirtide treatment. Although this is consistent with the proposed MBS item descriptor, the only change in management modelled due to the inclusion of HDV RNA monitoring was to cease treatment in non-responders at Week 144 (~33 months). The role of testing for monitoring the efficacy of bulevirtide is therefore not appropriately addressed in the economic model.*

Financial issues

- *The financial model has been updated to account for the changes requested following the March 2024 submission.*

ESCs discussion

The ESCs noted that this application was an integrated codependent re-submission seeking Medicare Benefits Schedule (MBS) listing of the quantitation of Hepatitis D viral ribonucleic acid (RNA) polymerase chain reaction (PCR) testing in plasma or serum to determine eligibility for treatment with bulevirtide in patients with chronic HDV (CHD) with compensated liver disease and for monitoring efficacy of bulevirtide treatment.

The ESCs noted that HDV infections occur within a setting of a co-infection with chronic hepatitis B virus (HBV). In Australia and in many countries globally, there is an effective HBV vaccination

program. Therefore, HDV infections are relatively rare and predominantly affect people who have immigrated to Australia.

The ESCs noted that bulevirtide is listed on the Australian Register of Therapeutic Goods (ARTG) for the treatment of CHD in adults with compensated liver disease. The ARTG listing cites the effectiveness of bulevirtide for the treatment of CHD being based on three randomised open-label studies, two completed Phase 2 studies and one ongoing Phase 3 study. In addition, a fourth ongoing randomised open-label Phase 2 study was included in the integrated analysis of clinical safety.

The ESCs noted that the mechanism of action of bulevirtide was to bind to and inactivate the viral receptor on the surface of hepatocytes that HDV uses to gain entry into the cells, thereby preventing virus entry into hepatocytes. The ESCs also noted that the reduction in viral load is dependent on hepatocyte replacement which is influenced by patient factors as well as viral factors and takes an extended period of time. Therefore, understanding the mechanism of action, and the link between viral load and hepatocyte replacement, is important for interpreting HDV load during the monitoring of treatment of CHD with bulevirtide. Thus the ESCs considered that there was biological plausibility to the claim that a quantitative test was required for monitoring of treatment of CHD with bulevirtide because a quantitative test is needed to detect reduction in viral load (relative to baseline) which is likely to precede a clinical response regardless of the absolute value. The ESCs noted that a qualitative test would not report viral load and is unlikely to be informative for monitoring. The ESCs also noted that resistance to bulevirtide is theoretically possible, although this was not discussed in the resubmission.

The ESCs noted that no consumer input had been received regarding this application.

The ESCs noted that the Department presented two possible sets of amendments to the applicant's proposed item descriptor. In the first set of amendments, while one item descriptor is retained, the reference to bulevirtide is replaced with a reference to a 'PBS listed treatment'. In the second (alternative) set of amendments, the Department proposed that in addition to replacing the reference to bulevirtide with a reference to a 'PBS listed treatment' there should be two separate MBS item descriptors, one for determining eligibility for treatment requestable by specialist or consultant physicians, and one for monitoring of response to treatment with no restriction on requestor type.

The ESCs considered that to maintain consistency with the recent approach to refer broadly to Pharmaceutical Benefits Scheme (PBS)-listed treatments, rather than to name the specific treatments, it was appropriate for the MBS item descriptor to refer to a treatment listed on the PBS, rather than to bulevirtide specifically.

The ESCs discussed the merits of restricting the MBS item for eligibility for treatment with bulevirtide to specialists, with the MBS item for monitoring being open to include non-specialists, such as general practitioners (GPs), as requestors. While the ESCs noted the Department's argument that opening the item for monitoring to non-specialists would potentially enable greater access to testing for patients, and allow GPs to be involved in ongoing management of CHD patients, the ESCs advised that as CHD is rare and the monitoring of HDV viral load and subsequent clinical management requires more highly specialised knowledge, the ordering of monitoring tests should also be limited to specialists. The ESCs also considered that restricting the ordering of monitoring tests to specialists would also make it more likely that sequential monitoring testing of the same patients would occur in the same laboratory, and thus reduce inter-laboratory variability in testing, if more laboratories were to take up this testing in the future. The ESCs suggested that the MBS item for monitoring HDV viral load during bulevirtide treatment should be limited to specialists, as has been proposed for the MBS item for testing for eligibility for treatment with bulevirtide, then there would be no need for two separate MBS items. Therefore, the ESCs recommended MSAC consider a single MBS item to cover testing for both eligibility and monitoring which is restricted to specialists.

Table 1 - Applicant's proposed MBS item for testing HDV RNA with Department's suggested amendments

Category 6 – PATHOLOGY SERVICES	
Group P3 - Microbiology	
MBS item *XXXX	
Quantitation of Hepatitis D viral RNA load in plasma or serum, is requested by a specialist or consultant physician for:	
1.1 The pre-treatment evaluation for access to therapy for chronic HDV in a patient who are is Hepatitis D viral antibody positive and suspected of having chronic hepatitis D, for access to a treatment listed on the Pharmaceutical Benefits Scheme (PBS); or 1.2 A patient undertaking viral therapy for chronic hepatitis D with bulevirtide a PBS listed treatment, for the purpose of assessing treatment effectiveness.	
To a maximum of 2 tests in a 12 month period	
Fee: \$152.10 Benefit: 75% \$114.10 85% = \$129.30	

Department suggested amendments in red text and strike-through

The ESCs noted that the concordance of quantitative tests could be problematic as the differences in viral loads measured by different commercial tests could be as large as 2 log₁₀IU/ml – which is the magnitude of change that the applicant argues is clinically meaningful. However, the ESCs noted that currently only one laboratory in Australia offers HDV RNA testing. This laboratory is the Victorian Infectious Diseases Reference Laboratory (VIDRL). VIDRL offers an in-house quantitative PCR test for the detection and quantification of HDV RNA. The ESCs noted that the in-house VIDRL assay has NATA accreditation for HDV testing. The in-house HDV RNA test has been validated against the World Health Organisation (WHO) reference standard for HDV genotype 1 and against other genotypes. Inter-run reproducibility of the in-house test used by VIDRL was demonstrated in the resubmission by testing low and high positive controls over seven runs. This demonstrated that the current test used in Australia is reproducible and measures viral load consistently. Moreover the ESCs considered that if other laboratories were to offer HDV testing in the future, an external quality assurance program (QAP) would ensure inter-laboratory consistency in testing. Under the *Requirements for Medical Pathology Services*, laboratories must be enrolled, participate and perform to an acceptable standard in external quality programs where they are available. Where such a program does not exist for a particular test method, the validity of the test results must be demonstrated by methods such as inter-laboratory comparisons or the analysis of reference material.

The ESCs also acknowledged that some variation of viral nucleic acid levels over time is to be expected when monitoring chronic viruses (e.g. HBV, HIV and HDV). The ESCs considered that the trends in HDV levels over time what was of ultimate importance in such testing and therefore the ESCs considered that the overall 'signal to noise' ratio of this proposed quantitative test was acceptable.

The ESCs noted that the key trial in this application was the MYR 301 trial, a phase 3 randomised trial of bulevirtide in patients with CHD. This trial concluded that after 48 weeks of bulevirtide treatment, HDV and ALT (alanine amino-transferase, a liver enzyme that indicates liver damage) levels were reduced in patients with CHD. The ESCs noted that the assay used in the key trial (Robogene ® RNA quantification kit) was different to the current quantitative HDV RNA assay available in Australia (an in-house assay available in a single Australian laboratory).

The ESCs noted the evidence presented in the resubmission. This included three studies that reported on the prognostic validity of HDV RNA detection versus no detection at baseline, two studies that looked at the ability of HDV RNA levels to predict the development of cirrhosis and four studies that looked at the relationship between a reduction in HDV viral load and associated health outcomes. The ESCs considered these supported the claim that active chronic HDV (detectable HDV RNA) was associated with worse liver-related outcomes.

The ESCs specifically noted a German study³¹ where 114 patients were treated with bulevirtide and the virological response was defined as a $>2 \log_{10}$ decline in viral load. Of the 114 treated patients, 87 (76%) had a virological response, with the mean time to virologic response being 23 weeks. In 11 cases, a virologic breakthrough ($>1 \log_{10}$ increase in HDV viral load) was observed. One out of the 114 patients treated with bulevirtide stopped treatment due to insufficient response, but it is not explicit whether this was due to lack of virological response (determined by HDV RNA). The ESCs noted that although this study potentially provides an example of a single case where treatment was altered due to the measurement of HDV RNA levels, the study was not informative regarding the proportion of patients with altered management in patients treated with bulevirtide, as the case series specifically excluded patients who had used bulevirtide in combination with pegylated interferon.

The ESCs identified an Austrian publication, Jachs et al 2022³², that was not identified in the resubmission (though an earlier abstract of this study was identified in the previous commentary). The ESCs considered this publication provided the most compelling evidence of likely changes in patient management as a result of monitoring quantitative HDV RNA levels in patients treated with bulevirtide. The ESCs noted that this study of 23 patients adopted a response-guided approach where patients who achieved virological response on bulevirtide monotherapy at week 24 continued this therapy and were offered to terminate treatment if HDV-RNA remained undetectable at least at three time points within 6 months while for patients without further HDV-RNA decline after week 24–48 interferon treatment was added irrespective of response. The study reported that interferon treatment was added in eight patients, comprising 2 viral responders with a $>2 \log_{10}$ or more reduction in HDV-RNA levels and 6 non-responders. The ESCs noted that a critical appraisal that was produced post-ESC concluded that the decision to change treatment by adding interferon for the two responders appeared to be directly related to the quantitative HDV RNA result. In the case of one patient interferon was added because of an increase in HDV-RNA at week 44, while for the other patient, interferon was added because there was no further reduction in HDV RNA after week 24. The ESCs also noted that the study indicated that for the second responder (who had interferon added to treatment because of an increase in viral load in week 44), the clinicians had expected a continued drop past $2 \log_{10}$ reduction over time. However, the critical appraisal noted that some non-responders received interferon and some did not and the reason for this discrepancy was not discussed in the study. The ESCs noted that interferon is not indicated for use in patients with HDV in Australia, although there are two PBS listings for peginterferon alfa-2a with unrestricted benefit listings.

The ESCs noted the pre-subcommittee response (PSCR) to the question of whether a qualitative test would be more appropriate for identification of eligible patients and monitoring efficacy of treatment with bulevirtide than a quantitative test. The PSCR stated that the resubmission has deliberately avoided using the term “undetectable” to define the HDV RNA level indicative of the response outcome of clinical relevance in CHD, because there have been significant improvements in the sensitivity of HDV RNA tests, over time. This means that patients reported in older studies as having undetectable levels of HDV RNA may have had detectable and quantifiable RNA levels using the current more advanced quantitative testing platforms. The ESCs acknowledged this argument and therefore accepted that the evidence presented in the resubmission including evidence based on detectable versus undetectable RNA levels was indicative of the biologically plausible claim that a drop in quantitative HDV viral load levels relative to baseline was indicative of clinical response to treatment insofar as patients with lower detectable viral loads may have a reduced risk of developing liver-related clinical events compared to patients with higher detectable viral loads. The ESCs also noted that quantitative testing is consistent with the current practices in testing of other chronic viruses that are not

³¹ Dietz-Fricke, et al (2023). “Treating hepatitis D with bulevirtide - Real-world experience from 114 patients.” JHEP Rep. Apr;5(4):100686

³² Jachs et al. (2022) “Response-guided long-term treatment of chronic hepatitis D patients with bulevirtide—results of a “real world” study.” Alimant Pharmacol Ther. 2022 May 5;56(1):144–154. doi: [10.1111/apt.16945](https://doi.org/10.1111/apt.16945)

rapidly cleared, including hepatitis B virus (HBV) and human immunodeficiency virus (HIV) and that quantitative RNA testing is also likely to be useful in determining non-responders to treatment (e.g. due to antiviral resistance or other factors).

Taking account of the above considerations and the additional evidence provided by Jachs et al (2022), the ESCs concluded that qualitative testing will result in the loss of valuable information while not necessarily being lower cost compared with quantitative testing. For these reasons, the ESCs advice to MSAC is that quantitative testing of HDV RNA levels was more appropriate for the monitoring of viral load both to identify eligible patients for treatment with bulevirtide as well as to determine the efficacy of treatment with bulevirtide than qualitative testing.

However, while noting the limitations of the concept of “detectable” vs “undetectable”, the ESCs considered the evidence provided did not adequately support the surrogacy of a $\geq 2 \log_{10}$ IU/mL decline in HDV RNA level, for improved long-term liver-related health outcomes. The ESCs noted that one publication provided evidence for this relationship (Farci et al 2004³³), however this analysis was based on data from a 1994 study of treatment with interferon, and two more recent studies (Palom 2021³⁴ and Wranke 2020³⁵) failed to show a statistically significant difference in clinical outcomes based on $\geq 2 \log_{10}$ IU/ml reduction. The ESCs noted that when PBAC considered entecavir for the treatment of CHB, it accepted the biological plausibility of the clinical relevance of reduction in viral load based on an outcome measure of an absolute reduction or reduction below a defined cut-off rather than a specified level of reduction in viral load.

The ESCs noted that the issues previously raised by the ESCs regarding the economic model remain largely unaddressed, and the model remains mostly unchanged. The ESCs noted that the ICER base case of \$ 95,000 to <\$115,000 per QALY assumed that the treatment response was a reduction in HDV RNA levels to undetectable HDV RNA levels or by $\geq 2 \log_{10}$ IU/mL, meaning that responders only had to meet one of these outcomes (linked to liver-related outcomes) but this was not the primary efficacy endpoint in the key trial (undetectable HDV RNA or decrease in HDV RNA levels by $\geq 2 \log_{10}$ IU/mL and ALT normalisation). The ESCs noted that a sensitivity analysis assuming response to treatment was the primary efficacy endpoint in the key trial increased the ICER by 11% to \$ 95,000 to <\$115,000 while assuming that the response was reduction to undetectable HDV RNA levels (i.e. all responders had to meet this more stringent outcome) increased the ICER by 56% to \$135,000 to <\$155,000 redacted. The ESCs considered the economic model was complex but had limited data to inform longer term costs and outcomes.

The ESCs noted that the economic model assumed that patients would undergo HDV RNA testing every 6 months while on bulevirtide treatment and that although this is consistent with the proposed MBS item descriptor, the model was limited because the only change in management modelled due to the inclusion of HDV RNA monitoring was to cease treatment in non-responders at Week 144. Nonetheless, the ESCs agreed that the clinical changes prompted by continued monitoring in the model were not specified and this issue was insufficiently addressed.

The ESCs noted that the financial model has been updated to account for the changes requested by MSAC following the March 2024 submission.

The ESCs advised that given the finding that a quantitative test that can determine viral load is an appropriate test for both initial testing and monitoring, the fee of \$152.10 is appropriate, being equivalent to quantitative testing fee for HBV (MBS item 69482 for the quantitation of HBV

³³ Farci, P, Roskams, T, Chessa, L, Peddis, G, Mazzoleni, AP, Scioscia, R, Serra, G, Lai, ME, Loy, M, Caruso, L, Desmet, V, Purcell, RH and Balestrieri, A 2004, 'Long-term benefit of interferon alpha therapy of chronic hepatitis D: regression of advanced hepatic fibrosis', *Gastroenterology*, vol. 126, no. 7, pp. 1740-1749.

³⁴ Palom A, Sopena S, et al. One-quarter of chronic hepatitis D patients reach HDV-RNA decline or undetectability during the natural course of the disease. *Alimentary Pharmacology & Therapeutics*. 2021;54(4):462-9.

³⁵ Wranke A, Lobato C, et al. Long-term outcome of hepatitis delta in different regions world-wide: Results of the Hepatitis Delta International Network. *Liver Int*. 2024;44(9):2442-57.

DNA). HBV testing was considered by the ESCs as an appropriate test against which to benchmark the proposed fee.

The ESCs advised that a critical appraisal of the new Austrian study by Jachs et al (2022) on change in management should be undertaken and provided to MSAC for its consideration. This critical appraisal was produced post-ESC and is provided in Section 9 of the Executive Summary and was discussed briefly above.

The ESCs noted that liver stiffness is measured via transient elastography (Fibroscan) and is useful in assessing liver fibrosis or scarring in patients with chronic liver disease. The ESCs noted that transient elastography is not currently MBS funded and patients currently pay privately for this service. The ESCs noted that an MSAC application was recently received for transient elastography, however it does not include the population with chronic liver disease due to hepatitis. The Department advised (out-of-session) that if MSAC ultimately recommended funding for this application in its current form, it would not facilitate access to an MBS rebate for transient elastography for any patients undergoing HDV RNA PCR testing.

17. Applicant comments on MSAC's Public Summary Document

Gilead welcomes the decision to support MBS listing of the HDV RNA PCR test for quantification of HDV RNA to i) determine eligibility for treatment with bulevirtide and ii) monitor the efficacy of bulevirtide treatment in patients with chronic HDV (CHD) infection with compensated liver disease. Gilead thanks the valuable input from multiple organisations who were all supportive of the public funding of this service.

18. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: [visit the MSAC website](#)