

Bulevirtide (chronic hepatitis D)

Benefit assessment according to §35a SGB V¹

EXTRACT

Project: A25-113 Version: 1.0 Status: 27 Nov 2025 DOI: 10.60584/A25-113_en

¹ Translation of Sections I 1 to I 6 of the dossier assessment *Bulevirtid (chronische Hepatitis D)* – *Nutzenbewertung gemäß § 35a SGB V*. Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Bulevirtide (chronic hepatitis D) – Benefit assessment according to §35a SGB V

Commissioning agency

Federal Joint Committee

Commission awarded on

1 September 2025

Internal Project No.

A25-113

DOI-URL

https://doi.org/10.60584/A25-113_en

Address of publisher

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Siegburger Str. 237
50679 Köln
Germany

Phone: +49 221 35685-0

Fax: +49 221 35685-1

E-mail: berichte@iqwig.de

Internet: www.iqwig.de

Recommended citation

Institute for Quality and Efficiency in Health Care. Bulevirtide (chronic hepatitis D); Benefit assessment according to §35a SGB V; Extract [online]. 2025 [Accessed: DD.MM.YYYY]. URL: https://doi.org/10.60584/A25-113_en.

Keywords

Bulevirtide, Hepatitis D – Chronic, Child, Adolescent, Adult, Benefit Assessment, NCT03852719

Medical and scientific advice

- Christoph F. Dietrich

IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

The questionnaire on the disease and its treatment was answered by Ingo van Thiel.

IQWiG thanks the respondent and the patient organization 'Deutsche Leberhilfe e. V.' for participating in the written exchange and for their support. The respondent and the 'Deutsche Leberhilfe e. V.' were not involved in the actual preparation of the dossier assessment.

IQWiG employees involved in the dossier assessment

- Sarah Hardebeck
- Simon Bogner
- Stefan Kobza
- Petra Kohlepp
- Philip Kranz
- Anne-Kathrin Petri
- Katherine Rascher
- Min Ripoll
- Sonja Schiller

Part I: Benefit assessment

I Table of contents

	Page
I List of tables	I.3
I List of abbreviations.....	I.4
I 1 Executive summary of the benefit assessment	I.1
I 2 Research question.....	I.9
I 3 Research question 1: adults with chronic HDV infection	I.10
I 3.1 Information retrieval and study pool.....	I.10
I 3.1.1 Studies included.....	I.11
I 3.1.2 Study characteristics.....	I.12
I 3.2 Results on added benefit	I.21
I 3.2.1 Outcomes included.....	I.21
I 3.2.2 Risk of bias	I.25
I 3.2.3 Results.....	I.27
I 3.2.4 Subgroups and other effect modifiers	I.32
I 3.3 Probability and extent of added benefit	I.33
I 3.3.1 Assessment of added benefit at outcome level	I.34
I 3.3.2 Overall conclusion on added benefit.....	I.37
I 4 Research question 2: children and adolescents (3 to < 18 years) with chronic HDV infection	I.38
I 4.1 Information retrieval and study pool.....	I.38
I 4.2 Results on added benefit	I.39
I 4.3 Probability and extent of added benefit	I.39
I 5 Probability and extent of added benefit – summary	I.40
I 6 References for English extract	I.41

I List of tables²

	Page
Table 2: Research questions for the benefit assessment of bulevirtide.....	I.1
Table 3: Bulevirtide – probability and extent of added benefit.....	I.8
Table 4: Research questions for the benefit assessment of bulevirtide.....	I.9
Table 5: Study pool – RCT, direct comparison: bulevirtide vs. BSC	I.12
Table 6: Characteristics of the study included – RCT, direct comparison: bulevirtide vs. no treatment.....	I.13
Table 7: Characteristics of the intervention – RCT, direct comparison: bulevirtide vs. no treatment.....	I.14
Table 8: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: bulevirtide vs. no treatment	I.18
Table 9: Risk of bias across outcomes (study level) – RCT, direct comparison: bulevirtide vs. no treatment	I.20
Table 10: Matrix of outcomes – RCT, direct comparison: bulevirtide vs. no treatment	I.22
Table 11: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: bulevirtide vs. no treatment.....	I.26
Table 12: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: bulevirtide vs. no treatment	I.28
Table 13: Subgroups (health-related quality of life) – RCT, direct comparison: bulevirtide vs. no treatment	I.33
Table 14: Extent of added benefit at outcome level: bulevirtide vs. BSC.....	I.35
Table 15: Positive and negative effects from the assessment of bulevirtide in comparison with BSC.....	I.37
Table 16: Bulevirtide – probability and extent of added benefit.....	I.40

² Table numbers start with “2” as numbering follows that of the full dossier assessment.

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
ALT	alanine aminotransferase
BSC	best supportive care
CTCAE	Common Terminology Criteria for Adverse Events
EMA	European Medicines Agency
FDA	Food and Drug Administration
FSS	Fatigue Severity Scale
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HDV	hepatitis delta virus
HIV	human immunodeficiency virus
HQLQ	Hepatitis Quality of Life Questionnaire
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
NA	nucleoside/nucleotide analogue
PCS	Physical Component Summary
PEG-IFN	peginterferon alfa-2a
PT	Preferred Term
RCT	randomized controlled trial
RNA	ribonucleic acid
SAE	serious adverse event
SF-36	Short Form 36 Health Survey
SGB	Sozialgesetzbuch (Social Code Book)
SMQ	Standardized MedDRA Query
SOC	System Organ Class
SVR	sustained virologic response
ULN	upper limit of normal

VAS	visual analogue scale
-----	-----------------------

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug bulevirtide. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the 'company'). The dossier was sent to IQWiG on 1 September 2025.

The drug in question is a drug for the treatment of an orphan condition. The company had to submit a dossier on the added benefit versus the appropriate comparator therapy (ACT) within 3 months after the request by the G-BA, because the turnover of the drug in the statutory health insurance had exceeded 30 million euros in the previous 12 calendar months.

Research question

The aim of this report is to assess the added benefit of bulevirtide compared with best supportive care (BSC) as the appropriate comparator therapy (ACT) for the treatment of chronic hepatitis delta virus (HDV) infection in plasma (or serum) HDV-RNA positive adult and paediatric patients 3 years of age and older weighing at least 10 kg with compensated liver disease.

The research questions presented in Table 2 were defined in accordance with the ACT specified by the G-BA.

Table 2: Research questions for the benefit assessment of bulevirtide

Research question	Therapeutic indication	ACT ^a
1	Adults with chronic HDV infection with compensated liver disease	Best supportive care ^{b, c}
2	Children and adolescents 3 to < 18 years of age weighing at least 10 kg with chronic HDV infection with compensated liver disease	Best supportive care ^{b, c}
a. Presented is the respective ACT specified by the G-BA. b. According to the G-BA, appropriate treatment of the underlying HBV infection corresponding to the generally accepted current state of medical knowledge is assumed; according to the S3 guideline, the use of PEG-IFN for the treatment of HBV infection should be considered in patients with chronic HBV/HDV co-infection. PEG-IFN is not authorized for the treatment of HDV infection. c. Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; HBV: hepatitis B virus; HDV: hepatitis delta virus; PEG-IFN: peginterferon alfa-2a		

If necessary for better readability, this benefit assessment uses the following terms for the patient populations of the research questions presented in Table 2:

- Research question 1: adults with chronic HDV infection
- Research question 2: children and adolescents (3 to < 18 years) with chronic HDV infection

Concurring with the G-BA, the company determined BSC as the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 48 weeks were used for the derivation of added benefit. This concurred with the company's inclusion criteria.

Research question 1: adults with chronic HDV infection

Study pool and study design

The study pool for this benefit assessment consisted of the completed, unblinded, multicentre, 3-arm study MYR301 comparing bulevirtide 2 mg versus bulevirtide 10 mg administered immediately or delayed for 48 weeks. The study comprised a 144-week treatment phase with a subsequent follow-up for 96 weeks. Adult patients (18 to 65 years) with chronic HBV/HDV co-infection were included in the study. At screening, patients had to have positive results for serum/plasma HDV RNA and have elevated alanine aminotransferase (ALT) ($> 1 \times$ upper limit of normal [ULN] and $< 10 \times$ ULN). Patients with decompensated liver disease or a Child-Pugh score above 7 points were excluded from the study. Furthermore, the use of interferon within the last 6 months prior to screening was prohibited.

A total of 150 patients were included in the study and randomly allocated in a 1:1:1 ratio to the study arms 2 mg bulevirtide (N = 49), 10 mg bulevirtide (N = 50), and delayed treatment with 10 mg bulevirtide starting at Week 49 (N = 51). Randomization was stratified according to the characteristic of cirrhosis at baseline (yes/no).

Treatment with bulevirtide 2 mg was administered in compliance with the recommendations in the summary of product characteristics (SmPC). The dosage of 10 mg bulevirtide per day is not covered by the marketing authorization; this treatment arm was therefore not taken into account for the benefit assessment. In the arm with the delayed administration of 10 mg bulevirtide, only the first 48 weeks, in which no treatment with bulevirtide was given, were relevant for the benefit assessment as a comparator arm. Thus, the first 48 weeks of the MYR301 study represented the relevant treatment and observation period for this benefit assessment. The HBV infection underlying the HDV infection was treated with nucleoside/nucleotide analogues (NAs) if indicated. The use of any other antiviral therapeutics, including peginterferon alfa-2a (PEG-INF), was prohibited in the study.

The primary outcome of the study was the combined response at Week 48, defined as undetectable HDV RNA ($< \text{limit of detection} = 6 \text{ IU/mL}$) or HDV RNA decrease by

$\geq 2 \log_{10}$ IU/mL compared with screening, and simultaneous ALT normalization. Moreover, outcomes were recorded in the categories morbidity, health-related quality of life and adverse events (AEs).

Data cuts

For this benefit assessment, the data for the observation period of 48 weeks of all patients from the last available data cut (4th data cut from 30 September 2022) were used for all relevant outcomes.

Implementation of the appropriate comparator therapy BSC

The G-BA specified BSC as ACT. The MYR301 study was not explicitly designed for a comparison with BSC, but the period relevant for the benefit assessment (48 weeks) was nevertheless used for the comparison with the G-BA's ACT. However, there were uncertainties regarding the implementation of BSC in accordance with the G-BA's specifications, particularly in the treatment of the underlying HBV infection. These uncertainties are explained below.

Treatment of the underlying HBV infection

According to the G-BA's notes, adequate treatment of the underlying HBV infection corresponding to the generally accepted current state of medical knowledge was assumed within the ACT. PEG-IFN and NAs are authorized for the treatment of chronic HBV infection and are recommended in the guidelines. According to national and international guidelines, the criteria for initiating therapy depend on the clinical parameters of the disease and the choice of therapy between NAs and PEG-IFN should be made on an individual basis, taking into account comorbidities and patient preference. In the MYR301 study, the therapeutic indication for the treatment of chronic HBV infection was based on guideline criteria, but treatment was permitted exclusively with NAs. A total of 63% of patients in the comparator arm were treated with NAs within the first 48 weeks. It is not possible to determine conclusively how many of these patients would have been treated with PEG-IFN rather than an NA if there had been free choice of treatment. Taking into account the patient characteristics, it was assumed that a relevant proportion of patients treated with NAs in the MYR301 study could also have received treatment for chronic HBV infection with PEG-IFN in accordance with marketing authorization requirements and clinical guidelines, and that such treatment would potentially have been provided within the German health care context. It should also be noted that although PEG-IFN is not approved for the treatment of HDV infection, it also shows activity against HDV infection. It was unclear how the option of treatment with PEG-IFN would have affected the results of the study. The certainty of conclusions of the results for all outcomes was therefore limited and no more than hints, e.g. of an added benefit, could be derived.

Risk of bias and certainty of conclusions

The risk of bias across outcomes was rated as low for MYR301.

The risk of bias of the results for the outcomes of overall survival, liver-related events, SAEs and severe AEs was assessed as low.

The risk of bias in the results relating to the outcomes of fatigue, health status, health-related quality of life, discontinuation due to AEs, and the specific AEs was assessed as high in each case.

Overall, at most hints, e.g. of an added benefit, can be derived for all outcomes on the basis of the effects shown in the MYR301 study.

Results

Mortality

Overall survival

No deaths occurred in the course of the study. There is no hint of an added benefit of bulevirtide in comparison with BSC for the outcome all-cause mortality; an added benefit is therefore not proven.

Morbidity

Liver-related events

There were no liver-related events during the course of the study. There is no hint of an added benefit of bulevirtide in comparison with BSC for the outcome liver-related events; an added benefit is therefore not proven.

Fatigue (FSS) and health status (EQ-5D VAS)

No statistically significant difference between the treatment groups was shown for the outcomes fatigue (recorded with the FSS) and health status (recorded with the EQ-5D VAS). In each case, there is no hint of an added benefit of bulevirtide in comparison with BSC; an added benefit is therefore not proven.

Health-related quality of life

HQLQ (SF-36) – Physical Component Summary (PCS)

No statistically significant difference between the treatment groups was shown for the PCS (recorded with the SF-36 of the HQLQ). There is no hint of an added benefit of bulevirtide in comparison with BSC; an added benefit is therefore not proven.

HQLQ (SF-36) – Mental Component Summary (MCS)

No statistically significant difference between the treatment groups was shown for the MCS (recorded with the SF-36 of the HQLQ). However, there was an effect modification for the characteristic of cirrhosis at baseline. There is a hint of an added benefit of bulevirtide in comparison with BSC for patients without cirrhosis at baseline. For patients with cirrhosis at baseline, there is no hint of an added benefit of bulevirtide in comparison with BSC.

HQLQ (hepatitis-specific questions) –health distress, positive well-being, hepatitis-specific health distress and hepatitis-specific limitations

No statistically significant difference between the treatment groups was shown for any of the outcomes of health distress, positive well-being, hepatitis-specific health distress and hepatitis-specific limitations (recorded with the hepatitis-specific questions of the HQLQ). In each case, there is no hint of an added benefit of bulevirtide in comparison with BSC; an added benefit is therefore not proven.

Side effects

SAEs and severe AEs

There was no statistically significant difference between the treatment arms for the outcomes of SAEs and severe AEs. There is no hint of greater or lesser harm of bulevirtide in comparison with BSC; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

There were no discontinuations due to AEs during the course of the study. There is no hint of greater or lesser harm of bulevirtide in comparison with BSC for the outcome discontinuation due to AEs; greater or lesser harm is therefore not proven.

Symptomatic increase of bile salts

No suitable data were available for the outcome of symptomatic increase of bile salts. There is no hint of greater or lesser harm of bulevirtide in comparison with BSC; greater or lesser harm is therefore not proven.

Other specific AEs

General disorders and administration site conditions (AEs)

A statistically significant difference to the disadvantage of bulevirtide in comparison with no treatment was shown for the outcome of general disorders and administration site conditions (AEs). There is a hint of greater harm of bulevirtide in comparison with BSC for this outcome.

Nervous system disorders (AEs)

A statistically significant difference to the disadvantage of bulevirtide in comparison with no treatment was shown for the outcome nervous system disorders (AEs). There is a hint of greater harm of bulevirtide in comparison with BSC for this outcome.

Research question 2: children and adolescents (3 to < 18 years) with chronic HDV infection

Transfer of results from adult patients from the RCT MYR301 to the target population not possible

Consistent with the findings of the company, the review of the completeness of the study pool did not produce any RCTs for this research question.

Due to the lack of RCTs for children and adolescents, the company conducted an information retrieval for adult patients in the given therapeutic indication. It did not conduct an information retrieval for further investigations in children and adolescents. For the assessment of the added benefit, the company sought to transfer study results from adult patients in the therapeutic indication to the paediatric population of this research question. As for research question 1, the company used study MYR301 and additionally study MYR202 for this purpose.

The company justified the transferability of the results from adults to the paediatric population with what it considered to be comparability of the disease profile, the mechanism of action and the clinical response under interferon therapy according to various criteria of the European Medicines Agency (EMA). The company added that the MYR301 study had also been used by the EMA for an evidence transfer from the adult to the paediatric population as part of the marketing authorization procedure for the paediatric population.

The company's approach of transferring study results from adult patients to the population of the given research question would be plausible in view of the lack of randomized comparative studies in paediatric patients. For the source population of adult patients in the therapeutic indication, the company conducted an information retrieval for RCTs. However, it did not conduct an information retrieval to identify all potentially relevant studies on the intervention or the ACT in the target population of this research question. There were therefore no studies or clinical data – neither comparative nor single-arm – for children and adolescents under the age of 18 to support the transferability of the results. Notwithstanding the points of criticism mentioned above, this benefit assessment did not determine any added benefit in the adult population based on the MYR301 study that could be transferred to the paediatric population.

The data presented by the company were not suitable for drawing conclusions on the added benefit of bulevirtide in comparison with BSC for the population of the research question at hand, i.e. children and adolescents (3 to < 18 years) with chronic HDV infection.

Results on added benefit

No suitable data were available for the assessment of the added benefit of bulevirtide in comparison with the ACT for plasma (or serum) HDV-RNA positive children and adolescents 3 to < 18 years of age weighing at least 10 kg with chronic HDV infection with compensated liver disease. There is no hint of an added benefit of bulevirtide in comparison with the ACT; an added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit³

On the basis of the results presented, the probability and extent of the added benefit of the drug bulevirtide versus the ACT is assessed as follows:

Research question 1: adults with chronic HDV infection

For research question 1 of this assessment, both positive and negative effects were shown for bulevirtide in comparison with BSC.

On the positive effects side, in the category of health-related quality of life, there is a hint of an added benefit with the extent 'major' for MCS for patients without cirrhosis at baseline. This positive effect was only shown on this scale of the generic questionnaire, but not on the disease-specific scales on health-related quality of life. Therefore, given the available data, the positive effect in the outcome MCS for patients without liver cirrhosis at baseline was not assessed as sufficient to justify a derivation of the added benefit separately by subgroup.

On the side of negative effects, in the category non-serious / non-severe side effects for the specific AEs general disorders and administration site conditions and nervous system disorders, there is a hint of greater harm with considerable extent. In the overall view of the available results, these negative effects in the specific AEs are not sufficient to justify a lesser benefit.

In summary, there is no hint of an added benefit of bulevirtide in comparison with the ACT BSC for plasma (or serum) HDV-RNA positive adult patients with chronic HDV infection with compensated liver disease.

³ On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Research question 2: children and adolescents (3 to < 18 years) with chronic HDV infection

Since no relevant study was available for this research question, there is no hint of an added benefit of bulevirtide in comparison with the ACT; an added benefit is therefore not proven.

Table 3 shows a summary of the probability and extent of the added benefit of bulevirtide.

Table 3: Bulevirtide – probability and extent of added benefit

Research question	Therapeutic indication	ACT ^a	Probability and extent of added benefit
1	Adults with chronic HDV infection with compensated liver disease	Best supportive care ^{b, c}	Added benefit not proven
2	Children and adolescents 3 to < 18 years of age weighing at least 10 kg with chronic HDV infection with compensated liver disease	Best supportive care ^{b, c}	Added benefit not proven
a. Presented is the respective ACT specified by the G-BA. b. According to the G-BA, appropriate treatment of the underlying HBV infection corresponding to the generally accepted current state of medical knowledge is assumed; according to the S3 guideline, the use of PEG-IFN for the treatment of HBV infection should be considered in patients with chronic HBV/HDV co-infection. PEG-IFN is not authorized for the treatment of HDV infection. c. Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; HBV: hepatitis B virus; HDV: hepatitis delta virus; PEG-IFN: peginterferon alfa-2a			

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

Supplementary note

The result of the assessment deviates from the result of the G-BA's assessment conducted in the context of the market launch in 2020, where the G-BA had determined a non-quantifiable added benefit of bulevirtide for plasma (or serum) HDV-RNA positive adults with chronic HDV infection with compensated liver disease. However, in the G-BA's assessment the added benefit was considered proven by the marketing authorization, regardless of the underlying data, due to the special situation for orphan drugs.

I 2 Research question

The aim of this report is to assess the added benefit of bulevirtide compared with best supportive care (BSC) as the appropriate comparator therapy (ACT) for the treatment of chronic hepatitis delta virus (HDV) infection in plasma (or serum) HDV-RNA positive adult and paediatric patients 3 years of age and older weighing at least 10 kg with compensated liver disease.

The research questions presented in Table 4 were defined in accordance with the ACT specified by the G-BA.

Table 4: Research questions for the benefit assessment of bulevirtide

Research question	Therapeutic indication	ACT ^a
1	Adults with chronic HDV infection with compensated liver disease	Best supportive care ^{b, c}
2	Children and adolescents 3 to < 18 years of age weighing at least 10 kg with chronic HDV infection with compensated liver disease	Best supportive care ^{b, c}
a. Presented is the respective ACT specified by the G-BA. b. According to the G-BA, appropriate treatment of the underlying HBV infection corresponding to the generally accepted current state of medical knowledge is assumed; according to the S3 guideline, the use of PEG-IFN for the treatment of HBV infection should be considered in patients with chronic HBV/HDV co-infection. PEG-IFN is not authorized for the treatment of HDV infection. c. Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; HBV: hepatitis B virus; HDV: hepatitis delta virus; PEG-IFN: peginterferon alfa-2a		

If necessary for better readability, this benefit assessment uses the following terms for the patient populations of the research questions presented in Table 4:

- Research question 1: adults with chronic HDV infection
- Research question 2: children and adolescents (3 to < 18 years) with chronic HDV infection

Concurring with the G-BA, the company determined BSC as the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 48 weeks were used for the derivation of added benefit. This concurred with the company's inclusion criteria.

I 3 Research question 1: adults with chronic HDV infection

I 3.1 Information retrieval and study pool

The study pool for the assessment was compiled on the basis of the following information:

Sources used by the company in the dossier:

- Study list on bulevirtide (status: 11 July 2025)
- Bibliographical literature search on bulevirtide (last search on 11 July 2025)
- Search of trial registries / trial results databases for studies on bulevirtide (last search on 11 July 2025)
- Search on the G-BA website for bulevirtide (last search on 11 July 2025)

To check the completeness of the study pool:

- Search of trial registries for studies on bulevirtide (last search on 15 September 2025); for search strategies, see I Appendix A of the full dossier assessment

The search did not identify any additional relevant studies.

Consistent with the findings of the company, MYR301 and MYR202 were identified as potentially relevant studies.

The company exclusively used the MYR301 study for the benefit assessment; this approach was appropriate. It presented the results of MYR202 [3] as supplementary information. It justified the exclusion of the MYR202 study on the grounds that the study duration of 24 weeks was too short. The exclusion of the MYR202 study was appropriate; however, in addition to the reasons for exclusion stated by the company, there were substantial deficiencies in the study design, as a result of which randomization of the included patients was not guaranteed. The following section describes the MYR202 study and explains why it was excluded.

MYR202

MYR202 is an open-label, parallel, multicentre, 4-arm phase 2 study comparing bulevirtide 2 mg, 5 mg or 10 mg + tenofovir disoproxil for 24 weeks followed by tenofovir disoproxil treatment alone for 24 weeks versus tenofovir disoproxil treatment alone for 48 weeks. A total of 120 adult patients (18 to 65 years) with chronic hepatitis B virus (HBV)/HDV co-infection were included in the study and allocated in a 1:1:1:1 ratio to the 4 study arms.

The company excluded the MYR202 study because the duration of the controlled comparison of bulevirtide versus the ACT (< 48 weeks) was too short. According to the company, the

required minimum duration of 48 weeks was based on the type of disease, the type of treatment, the mechanism of action of bulevirtide, the guideline recommendations and the G-BA's previous approach for comparable therapeutic indications such as HBV and human immunodeficiency virus (HIV).

The MYR202 study was not included in this benefit assessment, but this was primarily because substantial deficiencies in the study design meant that randomization was no longer considered to be guaranteed. For the MYR202 study, a 1:1:1:1 block randomization was originally planned. As of protocol version 5.0, a pharmacokinetic substudy was introduced in the Russian study centres, which was accompanied by a change in randomization. All patients who participated in the pharmacokinetic substudy after giving their consent could only be allocated to one of the 3 intervention arms (bulevirtide 2 mg, 5 mg or 10 mg + tenofovir disoproxil for 24 weeks, followed by tenofovir disoproxil for 24 weeks); randomization to the comparator arm (tenofovir disoproxil for 48 weeks) was excluded. Due to these restrictions, a total of 21% of the included patients were not randomly allocated to one of the 4 study arms. For a relevant proportion of study participants, allocation to an active treatment arm was therefore dependent on their consent to the pharmacokinetic substudy.

The inadequate randomization and inadequate allocation concealment was also criticized by the European Medicines Agency (EMA), as well as in the previous G-BA assessment of the drug bulevirtide [4,5]. The company also confirmed these deficiencies in its dossier and assessed the risk of bias at study level as high for this reason, among others.

Overall, appropriate randomization of patients to the treatment arms was not guaranteed in the MYR202 study. MYR202 was therefore not used for the benefit assessment.

I 3.1.1 Studies included

The study presented in the following table was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: bulevirtide vs. BSC

Study	Study category			Available sources		
	Study for the marketing authorization of the drug to be assessed (yes/no)	Sponsored study ^a (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries ^b (yes/no [citation])	Publication and other sources ^c (yes/no [citation])
MYR301	No	Yes ^d	No	Yes [6]	Yes [7,8]	Yes [4,9]
a. Study sponsored by the company. b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries. c. Other sources: documents from the search on the G-BA website and other publicly available sources. d. The initial study sponsor was completely taken over by the company in 2021. The company continued the MYR301 study after the takeover and is the marketing authorization holder for bulevirtide. ACT: appropriate comparator therapy; BSC: best supportive care; CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial						

The study pool was consistent with the study pool of the company.

I 3.1.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the study included – RCT, direct comparison: bulevirtide vs. no treatment^a (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes ^b
MYR301	RCT, open-label, parallel	Adults (18–65 years) with chronic HBV and HDV infection^c - Positive results for serum/plasma HDV RNA at screening - Elevated ALT (> 1 x ULN and < 10 x ULN) at screening	- bulevirtide 2 mg (N = 49) - No treatment for 48 weeks, followed by bulevirtide 10 mg (N = 51)^a - bulevirtide 10 mg (N = 50)^d	- Screening: 4 weeks - Treatment: 144 weeks - Follow-up: maximum up to 96 weeks after the end of treatment	16 centres in Germany, Italy, Russia and Sweden 4/2019–8/2024, randomization of the last patient: 12/2019 Data cut-offs: 1) 8 Jun 2020^{e, f} 2) 26 Nov 2020^{e, g, h} 3) 25 Oct 2021^{e, i} 4) 30 Sep 2022^{e, j}	Primary: Combined (virologic and biochemical) response^k at Week 48 Secondary: outcomes on morbidity, health-related quality of life, AEs

a. No treatment of chronic HDV infection for 48 weeks, followed by therapy with 10 mg bulevirtide for 96 weeks. The period of the first 48 weeks, during which no treatment with bulevirtide took place, is relevant for this benefit assessment. The irrelevant period is no longer shown in the following tables.

b. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.

c. Anti-HDV antibodies in serum or HDV RNA in serum/plasma for ≥ 6 months prior to screening

d. This arm is irrelevant for the assessment and is not presented in the following tables.

e. Discrepancy between information in Module 4 and in the CSR. The data cuts shown are based on the last visit of a patient included in the analysis and are taken from the CSR.

f. Interim analysis after 24 weeks of treatment.

g. Interim analysis after 48 weeks of treatment.

h. Due to laboratory samples being mixed up, a revised version of the CSR was prepared for this data cut, in which the virologic results for patients with confirmed mixed-up laboratory samples were imputed as missing values.

i. Interim analysis after 96 weeks of treatment.

j. Interim analysis at the end of treatment at Week 144.

k. Defined as undetectable HDV RNA (< LOD = 6 IU/mL) or HDV RNA decrease by ≥ 2 log₁₀ IU/mL compared with screening, and ALT normalization (depending on the central laboratory, Russian sites: ≤ 31 U/L for women and ≤ 41 U/L for men; all other sites ≤ 34 U/L for women and ≤ 49 U/L for men).

AE: adverse event; ALT: alanine aminotransferase; CSR: clinical study report; HBV: hepatitis B virus; HDV: hepatitis delta virus; LOD: limit of detection; N: number of randomized patients; RCT: randomized controlled trial; RNA: ribonucleic acid; ULN: upper limit of normal

Table 7: Characteristics of the intervention – RCT, direct comparison: bulevirtide vs. no treatment

Study	Intervention	Comparison
MYR301	bulevirtide 2 mg, SC, once daily Dose modifications ▪ No dose modification allowed ▪ Treatment interruption/discontinuation possible in the event of AEs^a Prior treatment <u>Allowed:</u> ▪ NAs for the treatment of chronic HBV infection <u>Not allowed:</u> ▪ interferon ≤ 6 months before screening Concomitant treatment <u>Allowed:</u> ▪ NAs for the treatment of chronic HBV infection^b <u>Not allowed^c:</u> ▪ Systemic glucocorticosteroids^d, immunomodulatory agents^e ▪ Other antiviral drugs for the treatment of HBV and/or HDV infection, apart from NAs ▪ Haematopoiesis-stimulating agents, (OATP)1B1 substrates^f, NTCP inhibitors^g	No treatment for HDV infection
a. According to the assessment of the investigator and in consultation with the clinical monitor. b. Patients who were already receiving an NA for chronic HBV infection continued their treatment during their participation in the study. For patients not receiving NAs for chronic HBV infection, treatment with an NA was initiated at the baseline visit or later in the study if indicated in accordance with international guidelines if one of following conditions was met: ▫ HBV DNA > 2000 IU/mL, ALT > ULN and/or at least moderate liver necroinflammation or fibrosis ▫ Liver cirrhosis with any detectable HBV DNA level ▫ HBV DNA > 20 000 IU/mL and ALT > 2 x ULN ▫ Family history of liver cirrhosis or hepatocellular carcinoma ▫ Extrahepatic manifestations of the HBV infection c. Exceptions possible if approved by the medical monitor. d. Inhaled glucocorticosteroids are allowed. e. Drugs intended for treatment of common cold are allowed. f. atorvastatin, bosentan, docetaxel, fexofenadine, glecaprevir, glyburide (glibenclamide), grazoprevir, nateglinide, paclitaxel, paritaprevir, pitavastatin, pravastatin, repaglinide, rosuvastatin, simeprevir, simvastatin, olmesartan, telmisartan, valsartan, voxilaprevir. g. sulfasalazine, irbesartan, ezetimibe, ritonavir, cyclosporine. AEs: adverse event; ALT: alanine aminotransferase; BSC: best supportive care; DNA: deoxyribonucleic acid; HBV: hepatitis B virus; OATP: organic anion transporting polypeptide; NA: nucleoside/nucleotide analogue; NTCP: sodium taurocholate cotransporting polypeptide; RCT: randomized controlled trial; ULN: upper limit of normal		

Study design

MYR301 is a completed, unblinded, multicentre, 3-arm RCT comparing bulevirtide 2 mg versus bulevirtide 10 mg administered immediately or delayed for 48 weeks. The completion and reporting of the MYR301 study by the company were obligations of the conditional marketing

authorization of bulevirtide granted by the EMA in 2020. In 2023, the conditional marketing authorization was converted to a regular marketing authorization following the submission of results from the MYR301 study at Week 48. The study comprised a 144-week treatment phase with a subsequent follow-up for 96 weeks. Adult patients (18 to 65 years) with chronic HBV/HDV co-infection were included in the study. At screening, patients had to have positive results for serum/plasma HDV RNA and have elevated alanine aminotransferase (ALT) ($> 1 \times$ upper limit of normal [ULN] and $< 10 \times$ ULN). Patients with decompensated liver disease or a Child-Pugh score above 7 points were excluded from the study. Furthermore, the use of interferon within the last 6 months prior to screening was prohibited.

A total of 150 patients were included in the study and randomly allocated in a 1:1:1 ratio to the study arms 2 mg bulevirtide (N = 49), 10 mg bulevirtide (N = 50), and delayed treatment with 10 mg bulevirtide starting at Week 49 (N = 51). Randomization was stratified according to the characteristic of cirrhosis at baseline (yes/no).

Treatment with bulevirtide 2 mg was administered in compliance with the recommendations in the summary of product characteristics (SmPC) [10]. The dosage of 10 mg bulevirtide per day is not covered by the marketing authorization; this treatment arm was therefore not taken into account for the benefit assessment. In the arm with the delayed administration of 10 mg bulevirtide, only the first 48 weeks, in which no treatment with bulevirtide was given, were relevant for the benefit assessment as a comparator arm. Thus, the first 48 weeks of the MYR301 study represented the relevant treatment and observation period for this benefit assessment. The HBV infection underlying the HDV infection was treated with nucleoside/nucleotide analogues (NAs) if indicated. The use of any other antiviral therapeutics, including peginterferon alfa-2a (PEG-INF), was prohibited in the study.

The primary outcome of the study was the combined response at Week 48, defined as undetectable HDV RNA ($< \text{limit of detection} = 6 \text{ IU/mL}$) or HDV RNA decrease by $\geq 2 \log_{10} \text{ IU/mL}$ compared with screening, and simultaneous ALT normalization. Moreover, outcomes were recorded in the categories morbidity, health-related quality of life and adverse events (AEs).

Data cuts

Four prespecified interim analyses were available for MYR301.

- 1st data cut (8 June 2020): interim analysis after 24 weeks of treatment/observation of all included patients
- 2nd data cut (26 November 2020): interim analysis after 48 weeks of treatment/observation of all included patients

- 3rd data cut (25 October 2021): interim analysis after 96 weeks of treatment/observation of all included patients
- 4th data cut (30 September 2022): interim analysis at the end of treatment (Week 144) of all included patients

According to the statistical analysis plan, an additional final analysis was planned after 240 weeks of observation of all included patients.

Only the first 48 weeks of the study, during which no treatment with bulevirtide was given in the comparator arm, were relevant for this benefit assessment. Only this period allowed a direct comparison of bulevirtide with the ACT. The data for the observation period of 48 weeks from the last available data cut (4th data cut from 30 September 2022) were used for all relevant outcomes.

Implementation of the appropriate comparator therapy BSC

The G-BA specified BSC as ACT. The MYR301 study was not explicitly designed for a comparison with BSC, but the period relevant for the benefit assessment (48 weeks) was nevertheless used for the comparison with the G-BA's ACT. Nevertheless, there were uncertainties as to whether BSC in accordance with the G-BA specifications was provided in the comparator arm. These uncertainties are explained below.

Treatment of the underlying HBV infection

According to the G-BA's notes, adequate treatment of the underlying HBV infection corresponding to the generally accepted current state of medical knowledge was assumed within the ACT. PEG-IFN and NAs are authorized for the treatment of chronic HBV infection and are recommended in the guidelines. The administration of PEG-IFN is associated with more side effects than that of NAs, but it is administered for a limited period and not as a long-term treatment like NAs. According to national and international guidelines, the criteria for initiating therapy depend on the clinical parameters of the disease and the choice of therapy between NAs and PEG-IFN should be made on an individual basis, taking into account comorbidities and patient preference [11-13]. In the MYR301 study, the therapeutic indication for the treatment of chronic HBV infection was based on guideline criteria, but treatment was permitted exclusively with NAs. A total of 63% of patients in the comparator arm were treated with NAs within the first 48 weeks. It is not possible to determine conclusively how many of these patients would have been treated with PEG-IFN rather than an NA if there had been free choice of treatment. Taking into account the patient characteristics (see Table 8), it was assumed that a relevant proportion of patients treated with NAs in the MYR301 study could also have received treatment for chronic HBV infection with PEG-IFN in accordance with marketing authorization requirements and clinical guidelines, and that such treatment would potentially have been provided within the German health care context. It should also be noted

that although PEG-IFN is not approved for the treatment of HDV infection, it also shows activity against HDV infection [14]. It was unclear how the option of treatment with PEG-IFN would have affected the results of the study. The certainty of conclusions of the results for all outcomes was therefore limited and no more than hints, e.g. of an added benefit, could be derived.

Further uncertainties in the implementation of BSC

In the MYR301 study, the administration of certain drugs, in particular statins (atorvastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin) and sartans (olmesartan, telmisartan, valsartan, irbesartan) was prohibited due to their interaction potential with bulevirtide. The medication classes listed represent relevant medications for common comorbidities in everyday practice. It should also be noted that a total of 57% of all randomized patients in the MYR301 study were enrolled by treatment centres in Russia and 43% in Germany, Italy or Sweden. It was difficult to assess to which extent treatment in the comparator arm of the study in Russia corresponded to the implementation of BSC in the German health care context. In its dossier, the company presented subgroup analyses for the characteristic region (Germany/Italy/Sweden versus Russia). There were no effect modifications for the characteristic region in the outcomes relevant for this benefit assessment.

Overall, possible regional differences in the implementation of BSC and the prohibition of certain drugs represented an additional uncertainty in the MYR301 study; however, in light of the prohibition of PEG-IFN therapy described above, this was of secondary importance.

Characteristics of the study population

Table 8 shows the patient characteristics of the included study.

Table 8: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: bulevirtide vs. no treatment (multipage table)

Study Characteristic Category	bulevirtide N = 49	No treatment N = 51
MYR301		
Age [years], mean (SD)	44 (9)	41 (8)
Sex [F/M], %	39/61	49/51
Family origin, n (%)		
Asian	8 (16)	11 (22)
White	41 (84)	40 (78)
Cirrhosis status, n (%)		
Yes	23 (47)	24 (47)
No	26 (53)	27 (53)
Child-Pugh class of cirrhosis		
A	23 (47 ^a)	24 (47 ^a)
B	0 (0)	0 (0)
C	0 (0)	0 (0)
METAVIR fibrosis stage, n (%)		
< F2	20 (41) ^{a, b}	16 (31) ^{a, b}
≥ F2	9 (18) ^{a, b}	16 (31) ^{a, b}
Information missing	20 (41) ^{a, b}	19 (37) ^{a, b}
HDV RNA at baseline (log ₁₀ IU/mL)		
Mean (SD)	5.1 (1.2)	5.1 (1.4)
Median [min; max]	5.2 [2.0; 7.1]	5.4 [1.4; 7.5]
HDV-1 genotype, n (%)		
Genotype HDV-1	49 (100)	51 (100)
ALT (U/L) at baseline		
Mean (SD)	107.9 (62.5)	101.6 (61.9)
Median [min; max]	90.0 [31; 302]	80.0 [39; 273]
Liver stiffness (kPa)		
Mean (SD)	14.0 (8.2)	15.3 (9.0)
Median [min; max]	12.0 [4.3; 46.4]	11.9 [5.8; 41.6]
HBV DNA at baseline (log ₁₀ IU/mL)		
Mean (SD)	1.3 (1.3)	0.9 (1.0)
Median [min; max]	1.3 [0.0; 6.3]	1.0 [0.0; 3.8]
Qualitative HBV DNA at baseline		
Positive	14 (29)	13 (25)
Negative	12 (24)	12 (24)
Missing	23 (47)	26 (51)
History of oral HBV treatment ^{c, d}	15 (31)	15 (29)

Table 8: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: bulevirtide vs. no treatment (multipage table)

Study Characteristic Category	bulevirtide N = 49	No treatment N = 51
History of interferon therapy ^e , n (%)	26 (53)	29 (57)
Concomitant oral HBV treatment ^{c, f}	32 (65)	32 (63)
HBsAg at baseline (log ₁₀ IU/mL)		
Mean (SD)	3.7 (0.5)	3.7 (0.5)
Median [min; max]	3.7 [2.3; 4.5]	3.7 [2.5; 4.4]
HBeAg status at baseline, n (%)		
Positive	4 (8)	4 (8)
Negative	45 (92)	47 (92)
Alcohol consumption, n (%)		
Current user	7 (14)	4 (8)
Former user	12 (24)	9 (18)
Non-user	30 (61)	38 (75)
Drug use, n (%)		
Current user	0 (0)	0 (0)
Former user	0 (0)	0 (0)
Non-user	49 (100)	51 (100)
Treatment discontinuation, n (%) ^g	ND ^h	ND
Study discontinuation, n (%) ^{g, i}	1 (2 ^a)	1 (2 ^a)
a. Institute's calculation. b. There are discrepant data between Module 4 A and the CSR; the numbers from the CSR are shown. c. The following drugs were considered: tenofovir, tenofovir alafenamide, tenofovir disoproxil fumarate, entecavir, adefovir, lamivudine or telbivudine. d. Discontinued before baseline. e. According to inclusion and exclusion criteria discontinued at least 6 months before baseline. f. Includes patients who were already treated with NAs at randomization as well as patients in whom NA therapy was newly initiated at baseline according to the study criteria (see Table 7). g. Up to Week 48. h. Since the minimum treatment duration with bulevirtide in the intervention group (including the patient with study discontinuation) was 46.4 weeks, it is assumed that, apart from one study discontinuation, there was no further treatment discontinuation before the end of Week 48. i. 1 person in the intervention arm withdrew their consent and 1 person in the comparator arm discontinued the study early due to pregnancy. ALT: alanine aminotransferase; CSR: clinical study report; DNA: deoxyribonucleic acid; F: female; HBeAg: hepatitis B e antigen; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus; HDV: hepatitis delta virus; M: male; max: maximum; min: minimum; n: number of patients in the category; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; RNA: ribonucleic acid; SD: standard deviation		

The demographic and clinical characteristics of the patients in both treatment arms of the MYR301 study were largely comparable. The mean patient age was 44 versus 41 years, and

most patients were of white family origin (84% versus 78%). The proportion of male study participants was slightly higher in the intervention arm than in the comparator arm (61% versus 51%). In both study arms, 47% of patients had cirrhosis at baseline. The average HDV RNA at baseline was 5.1 log₁₀ IU/mL in both arms. The average HBV DNA at baseline was slightly higher in the intervention arm than in the comparator arm (1.3 versus 0.9 log₁₀ IU/mL). In both study arms, about half of the patients had completed previous treatment with interferon (53% versus 57%) and about one third of the patients had completed previous HBV treatment with NAs (31% versus 29%). Concomitant HBV treatment with NAs was provided to 65% of patients in the intervention arm and 63% of patients in the comparator arm during the first 48 weeks of the study. There was one study discontinuation in both study arms. The company did not provide any additional information on the number of patients who discontinued treatment. However, it could be concluded from the information on the minimum treatment duration that there were no premature treatment discontinuations in the MYR301 study.

Risk of bias across outcomes (study level)

Table 9 shows the risk of bias across outcomes (risk of bias at study level).

Table 9: Risk of bias across outcomes (study level) – RCT, direct comparison: bulevirtide vs. no treatment

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	Absence of other aspects	Risk of bias at study level
			Patients	Treating staff			
MYR301	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low for MYR301. Limitations resulting from the open-label study design are described in Section I 3.2.2 under outcome-specific risk of bias.

Transferability of the study results to the German health care context

The company stated that the study results of MYR301 were transferable to everyday health care in Germany due to the comparability of the study population and the HDV-infected German population.

Referring to the information provided by the Robert Koch Institute, the company explained that HDV infection mainly affects people in middle age and rarely people aged < 25 und > 65 years, and that men are affected slightly more often than women. According to the

company, in the MYR301 study, the mean age of participants infected with HDV was 44 years (intervention arm) and 41 years (comparator arm), and more men than women were included in the study (61% and 51% respectively). It added that, in line with the proportions in the population in Germany, at least 78% of patients were white.

The company further stated that the MYR301 study was conducted in Germany, Italy, Russia and Sweden and assumed comparable study conditions in the centres, particularly with regard to the study medications and concomitant medications.

The company did not provide any further information on the transferability of the study results to the German health care context. For the transferability of the study results, see also Section I 3.1.1.

I 3.2 Results on added benefit

I 3.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
 - All-cause mortality
- Morbidity
 - Liver-related events
 - Fatigue, recorded with the Fatigue Severity Scale (FSS)
 - Health status, recorded using the EQ-5D visual analogue scale (VAS)
- Health-related quality of life
 - recorded with the Hepatitis Quality of Life Questionnaire (HQLQ), consisting of the Short Form 36 Health Survey (SF-36) and 15 additional hepatitis-specific questions
- Side effects
 - Serious adverse events (SAEs)
 - Severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
 - Discontinuation due to AEs
 - Symptomatic increase of bile salts
 - Other specific AEs, if any

The selection of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4).

Table 10 shows for which outcomes data were available in the included study.

Table 10: Matrix of outcomes – RCT, direct comparison: bulevirtide vs. no treatment

Study	Outcomes									
	All-cause mortality ^a	Liver-related events ^{b, c}	Fatigue (FSS)	Health status (EQ-5D VAS)	Health-related quality of life (HQLQ ^d)	SAEs	Severe AEs ^e	Discontinuation due to AEs	Symptomatic increase of bile salts	Other specific AEs ^f
MYR301	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No ^g	Yes
a. The results on all-cause mortality are based on the information on fatal AEs. b. Defined as cirrhosis development, development or worsening of jaundice, coagulopathy, ascites, hepatic encephalopathy or bleeding from oesophageal varices, hepatocellular carcinoma development, liver transplantation, liver-related hospitalization or liver-related death. c. Due to the observation period of 48 weeks, the informative value of this outcome is limited. d. Consisting of the SF-36 and 15 additional hepatitis-specific questions. e. Operationalized as CTCAE grade ≥ 3. f. The following events (MedDRA coding) are considered: general disorders and administration site conditions (SOC, AEs) and nervous system disorders (SOC, AEs). g. No suitable data available; see running text for reasons. AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; FSS: Fatigue Severity Scale; HQLQ: Hepatitis Quality of Life Questionnaire; MedDRA: Medical Dictionary for Regulatory Activities; RCT: randomized controlled trial; SAE: serious adverse event; SF-36: Short Form 36; SOC: System Organ Class; VAS: visual analogue scale										

Notes on outcomes

Virologic and biochemical response

The primary outcome of the MYR301 study was the combined response, defined as the simultaneous occurrence of a virologic response (undetectable HDV RNA or decrease in viral load by $\geq 2 \log_{10}$ IU/mL) and biochemical response (normalization of alanine aminotransferase). The company used the outcome of combined response and its individual components for the derivation of the added benefit and described these outcomes as surrogates for the prevention of liver-related morbidity (liver fibrosis, liver cirrhosis, liver decompensation, development of hepatocellular carcinoma [HCC]) and mortality.

The company did not present a surrogate validation study for the combined response or its individual components. Instead, with reference to various publications, it described in text form that the association between the surrogate outcomes presented and patient-relevant

outcomes was “qualitatively proven”, but that the extent of the correlation was “not yet quantifiable”.

In certain situations, the validity of a surrogate outcome may be considered sufficient even without the existence of a surrogate validation study. Such a situation exists, for example, in the therapeutic indication of chronic hepatitis C, where sustained virologic response (SVR) under antiviral therapy has been recognized as a sufficiently valid surrogate for the patient-relevant outcome of prevention of HCC [15]. This was based on the successful demonstration of a substantial risk reduction for HCC with an SVR achieved after treatment (relative risk [95% confidence interval] = 0.21 [0.16; 0.27]) and an associated equalization of the risk with that of the healthy population [16].

The situation here was not comparable. The company referred to studies in which an association between HDV viral load and clinical outcomes was described. The quality of the cited studies was heterogeneous and the operationalization of the surrogate outcomes considered in these varied greatly. Patients with low viral load after therapy and low viral load at baseline were often considered together. The company’s dossier did not provide a quantitative presentation of high methodological quality showing the risk reduction in patients under treatment who achieved the surrogate outcomes used in the dossier, and such a presentation also did not appear feasible based on the data described.

In addition, there is also no consensus among experts on how virologic response or combined response in HDV infection correlates with longer-term clinical outcomes [17-20]. This applies in particular to the outcome of decrease in viral load by $\geq 2 \log_{10}$. In the Food and Drug Administration (FDA) guidance on developing drugs for the treatment of chronic HDV infection cited by the company, the outcome combined response is described as a surrogate outcome. According to the FDA, however, this surrogate outcome is only acceptable in the accelerated approval process and requires subsequent confirmation using a clinical outcome such as cirrhosis, HCC or liver-related death [21].

In summary, it can be determined that it is not clear from the company’s explanations that the surrogate outcomes presented – combined, virologic or biochemical response – are valid surrogates for patient-relevant outcomes in patients with HDV infection. These outcomes were therefore not used to derive the added benefit in this benefit assessment. Results on these outcomes are presented as supplementary information in I Appendix B of the full dossier assessment.

Liver-related events

The aim of treatment of chronic HDV infection is to prevent patient-relevant liver-related events such as the development of hepatocellular carcinoma and liver-related death. In the MYR301 study, the composite outcome of liver-related clinical events was recorded, defined

as cirrhosis development, development or worsening of jaundice, coagulopathy, ascites, hepatic encephalopathy or bleeding from oesophageal varices, hepatocellular carcinoma development, liver transplantation, liver-related hospitalization or liver-related death. This outcome included patient-relevant liver-related events, but also events defined by laboratory tests whose direct patient relevance is not certain (e.g. coagulopathy). Since no events occurred in either arm of the MYR301 study during the observation period relevant for the benefit assessment, and thus no non-patient-relevant events, the outcome liver-related clinical events was used in the given data situation. The informative value of the results on liver-related events was limited overall by the comparative observation period of the study of a total of 48 weeks.

Patient-reported outcomes

For all patient-reported outcomes, the company presented analyses on improvement of at least 15% of the scale range at Week 48, which were used for the benefit assessment. Analyses regarding deterioration were not available.

Fatigue

In its dossier, the company presented results on the outcome fatigue, recorded using the FSS. The FSS is a generic questionnaire for assessing the severity of fatigue symptoms and their impact on the patient's everyday life. The FSS consists of 9 items that are assessed on a 7-point scale (1 = complete disagreement with the statement; 7 = complete agreement) [22]. Higher values indicate a higher level of fatigue. The FSS was recorded at Weeks 0, 24, 40 and 48. In its dossier, the company presented non-prespecified responder analyses on the improvement of at least 15% of the scale range at Week 48. This analysis was used for this benefit assessment.

Health-related quality of life

In its dossier, the company presented results on health-related quality of life, recorded using the HQLQ in version 2 (HQLQ-v2). The HQLQ is a questionnaire developed to assess the generic and disease-specific well-being of patients with chronic hepatitis C [23]. The HQLQ-v2 consists of the SF-36 and 4 other hepatitis-associated domains. The HQLQ-v2 comprises a total of 51 items, 36 items of the SF-36 and 15 additional items, which are organized in the 4 domains of health distress, positive well-being, hepatitis-specific health distress and hepatitis-specific limitations, and are referred to in this benefit assessment as 'hepatitis-specific questions'. Version 2 of the HQLQ used by the company is a shortened version with only 51 instead of 69 items. No information was available on how the number of items was reduced. However, the content validity of the HQLQ-v2 was comprehensively investigated by Lampertico et al. [24]. Based on this investigation, the content validity of the HQLQ-v2 was assessed as sufficient for patients with chronic HDV infection to represent the disease-specific health-related quality of life.

The HQLQ was recorded at Weeks 0, 24, 40 and 48. For the SF-36 and the 4 additional scales, the company presented responder analyses for the proportion of patients with an improvement of at least 15% of the scale range at Week 48. This analysis was used for this benefit assessment.

Symptomatic increase of bile salts

The mechanism of action of bulevirtide can lead to inhibition of the bile salt transporter in the hepatocytes, which is accompanied by a dose-dependent increase in bile acids in the blood [3]. In the MYR301 study, an increase in bile salts is captured by the Preferred Term (PT) 'bile salts increased', coded according to the Medical Dictionary for Regulatory Activities (MedDRA). In accordance with the study protocol, only events that were assessed as symptomatic and clinically significant were taken into account. A total of 1 versus 0 events occurred in the PT 'bile salts increased' (AEs). The PT 'bile salts increased' is not a suitable operationalization for the outcome symptomatic increase of bile salts. For example, a predefined Standardized MedDRA Query (SMQ) that takes into account typical symptoms caused by an increase of bile salts, such as itching, headache or nausea, would have been suitable for recording the outcome. Such an analysis was not available.

I 3.2.2 Risk of bias

Table 11 describes the risk of bias for the results of the relevant outcomes.

Table 11: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: bulevirtide vs. no treatment

Study	Study level	Outcomes									
		All-cause mortality ^a	Liver-related events ^{b, c}	Fatigue (FSS)	Health status (EQ-5D VAS)	Health-related quality of life (HQLQ ^d)	SAEs	Severe AEs ^e	Discontinuation due to AEs	Symptomatic increase of bile salts	Other specific AEs ^f
MYR301	L	L	L	H ^g	H ^g	H ^g	L	L	H ^h	L ⁱ	H ^g

a. The results on all-cause mortality are based on the information on fatal AEs.
 b. Defined as cirrhosis development, development or worsening of jaundice, coagulopathy, ascites, hepatic encephalopathy or bleeding from oesophageal varices, hepatocellular carcinoma development, liver transplantation, liver-related hospitalization or liver-related death.
 c. Due to the observation period of 48 weeks, the informative value of the results of this outcome is limited.
 d. Consisting of the SF-36 and 15 additional hepatitis-specific questions.
 e. Operationalized as CTCAE grade ≥ 3 .
 f. The following events (MedDRA coding) are considered: general disorders and administration site conditions (SOC, AEs) and nervous system disorders (SOC, AEs).
 g. Lack of blinding in the presence of subjective recording of outcomes.
 h. Lack of blinding in the presence of subjective decision on treatment discontinuation.
 i. No suitable data available; for reasoning, see Section I 3.2.1 of this dossier assessment.
 AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; FSS: Fatigue Severity Scale; H: high; HQLQ: Hepatitis Quality of Life Questionnaire; L: low; MedDRA: Medical Dictionary for Regulatory Activities; RCT: randomized controlled trial; SAE: serious adverse event; SF-36: Short Form 36; SOC: System Organ Class; VAS: visual analogue scale

The risk of bias of the results for the outcomes of overall survival, liver-related events, SAEs and severe AEs was assessed as low.

The MYR301 study is an open-label RCT. Due to the associated lack of blinding in the presence of subjective outcome recording, the risk of bias was assessed as high for the results of the following patient-reported outcomes: fatigue (recorded with the FSS), health status (recorded with the EQ-5D VAS), health-related quality of life (recorded with the HQLQ, consisting of the SF-36 and 15 additional hepatitis-specific questions) and the specific AEs (general disorders and administration site conditions [AEs] and nervous system disorders [AEs]).

The results of the outcome of discontinuation due to AEs had a high risk of bias because of lack of blinding in subjective decisions regarding treatment discontinuation.

Summary assessment of the certainty of conclusions

According to the G-BA's notes, appropriate treatment of the underlying HBV infection corresponding to the generally accepted current state of medical knowledge was assumed. The administration of PEG-INF or NAs is recommended for the treatment of chronic HBV infection. In the MYR301 study, only the use of NAs was permitted for the treatment of HBV infection; treatment with PEG-INF was prohibited. In the MYR301 study, treatment with NAs in the comparator arm may not have been the most suitable treatment for the underlying HBV infection for a relevant proportion of patients (for a detailed explanation, see the text section on treatment of the underlying HBV infection in Section I 3.1.2). This reduced the certainty of conclusions of the study results. Based on the available information from the MYR301 study, at most hints, e.g. of an added benefit, could be derived for all outcomes presented.

I 3.2.3 Results

Table 12 summarizes the results from the comparison of bulevirtide versus no treatment in plasma (or serum) HDV-RNA positive adult patients with chronic HDV infection with compensated liver disease. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

The additional results presented for the surrogate outcomes of combined, virologic and biochemical response can be found in I Appendix B of the full dossier assessment. The results on common AEs, common SAEs and common severe AEs are presented in I Appendix C of the full dossier assessment.

Table 12: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: bulevirtide vs. no treatment (multipage table)

Study Outcome category Outcome	bulevirtide		No treatment		bulevirtide vs. no treatment
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value ^a
MYR301 (Week 48)					
Mortality					
All-cause mortality ^b	49	0 (0)	51	0 (0)	–
Morbidity					
Liver-related events ^c	49	0 (0) ^d	51	0 (0)	–
Fatigue (FSS – improvement at Week 48 ^e)	49	20 (40.8)	51	13 (25.5)	1.60 [0.90; 2.85]; 0.121
Health status (EQ-5D VAS – improvement at Week 48 ^e)	49	17 (34.7)	51	13 (25.5)	1.36 [0.74; 2.50]; 0.364
Health-related quality of life					
HQLQ ^f (SF-36 – improvement at Week 48 ^e)					
Physical Component Summary (PCS)	49	4 (8.2)	51	3 (5.9)	1.39 [0.33; 5.88]; 0.717
Mental Component Summary (MCS)	49	13 (26.5)	51	8 (15.7)	1.69 [0.77; 3.72]; 0.222
Physical functioning	49	11 (22.4)	51	10 (19.6)	1.14 [0.53; 2.45]
Physical role functioning	49	15 (30.6)	51	8 (15.7)	1.95 [0.91; 4.19]
Physical pain	49	14 (28.6)	51	14 (27.5)	1.04 [0.56; 1.95]
General health perception	49	16 (32.7)	51	15 (29.4)	1.11 [0.62; 1.99]
Vitality	49	14 (28.6)	51	10 (19.6)	1.46 [0.72; 2.97]
Social functioning	49	12 (24.5)	51	6 (11.8)	2.08 [0.85; 5.11]
Emotional role functioning	49	19 (38.8)	51	16 (31.4)	1.24 [0.72; 2.11]
Mental well-being	49	18 (36.7)	51	15 (29.4)	1.25 [0.71; 2.19]

Table 12: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: bulevirtide vs. no treatment (multipage table)

Study Outcome category Outcome	bulevirtide		No treatment		bulevirtide vs. no treatment
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value ^a
HQLQ ^f (hepatitis-specific questions – improvement at Week 48 ^e)					
Health distress	49	24 (49.0)	51	18 (35.3)	1.39 [0.87; 2.22]; 0.222
Positive well-being	49	11 (22.4)	51	11 (21.6)	1.04 [0.50; 2.18]; 0.948
Hepatitis-specific health distress	49	28 (57.1)	51	23 (45.1)	1.27 [0.86; 1.87]; 0.250
Hepatitis-specific limitations	49	16 (32.7)	51	8 (15.7)	2.08 [0.98; 4.42]; 0.057
Side effects					
AEs (supplementary information)	49	41 (83.7)	51	41 (80.4)	–
SAEs	49	2 (4.1)	51	1 (2.0)	2.08 [0.19; 22.23]; 0.598
Severe AEs ^h	49	5 (10.2)	51	4 (7.8)	1.30 [0.37; 4.56]; 0.771
Discontinuation due to AEs	49	0 (0)	51	0 (0)	–
Symptomatic increase of bile salts				No suitable data ⁱ	
General disorders and administration site conditions (SOC, AEs)	49	15 (30.6)	51	2 (3.9)	7.81 [1.88; 32.37]; < 0.001
Nervous system disorders (SOC, AEs)	49	11 (22.4)	51	0 (0)	23.92 ^j [1.45; 395.20]; < 0.001

Table 12: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: bulevirtide vs. no treatment (multipage table)

Study Outcome category Outcome	bulevirtide		No treatment		bulevirtide vs. no treatment
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value ^a
a. Institute's calculation of RR, CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [25]). In case of zero events in one study arm, the correction factor 0.5 was used for the calculation of effect and CI in both study arms. b. The results on all-cause mortality are based on the data on fatal AEs. c. Defined as cirrhosis development, development or worsening of jaundice, coagulopathy, ascites, hepatic encephalopathy or bleeding from oesophageal varices, hepatocellular carcinoma development, liver transplantation, liver-related hospitalization or liver-related death. d. On Study Day 150, one patient had a liver-related hospitalization for oesophageal varices planned before the start of the study. e. A score increase by $\geq 15\%$ of the scale range from baseline is considered a clinically relevant improvement. f. Consisting of the SF-36 and 15 additional hepatitis-specific questions. g. An increase in PCS by ≥ 9.45 points or in MCS by ≥ 9.6 points from baseline is considered a clinically relevant improvement (scale range: 7.3 to 70.1 for PCS and 5.8 to 69.9 for MCS; determined using the 2009 norm sample [26]). h. Operationalized as CTCAE grade ≥ 3. i. See Section I 3.2.1 of this dossier assessment for the reasoning. j. This effect is largely determined by the difference with regard to the PT headache (9 vs. 0). AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z-score; CTCAE: Common Terminology Criteria for Adverse Events; FSS: Fatigue Severity Scale; HQLQ: Hepatitis Quality of Life Questionnaire; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SF-36: Short Form 36; SOC: System Organ Class; VAS: visual analogue scale					

On the basis of the available information, no more than hints, e.g. of an added benefit, can be determined for all outcomes.

Mortality

All-cause mortality

No deaths occurred in the course of the study. There is no hint of an added benefit of bulevirtide in comparison with BSC for the outcome all-cause mortality; an added benefit is therefore not proven.

Morbidity

Liver-related events

There were no liver-related events during the course of the study. There is no hint of an added benefit of bulevirtide in comparison with BSC for the outcome liver-related events; an added benefit is therefore not proven.

Fatigue (FSS) and health status (EQ-5D VAS)

No statistically significant difference between the treatment groups was shown for the outcomes fatigue (recorded with the FSS) and health status (recorded with the EQ-5D VAS). In each case, there is no hint of an added benefit of bulevirtide in comparison with BSC; an added benefit is therefore not proven.

Health-related quality of life

HQLQ (SF-36)

Physical Component Summary (PCS)

No statistically significant difference between the treatment groups was shown for the PCS (recorded with the SF-36 of the HQLQ). There is no hint of an added benefit of bulevirtide in comparison with BSC; an added benefit is therefore not proven.

Mental Component Summary (MCS)

No statistically significant difference between the treatment groups was shown for the MCS (recorded with the SF-36 of the HQLQ). However, there was an effect modification for the characteristic of cirrhosis at baseline (see Section I 3.2.4). There is a hint of an added benefit of bulevirtide in comparison with BSC for patients without cirrhosis at baseline. For patients with cirrhosis at baseline, there is no hint of an added benefit of bulevirtide in comparison with BSC.

HQLQ (hepatitis-specific questions)

Health distress, positive well-being, hepatitis-specific health distress and hepatitis-specific limitations

No statistically significant difference between the treatment groups was shown for any of the outcomes of health distress, positive well-being, hepatitis-specific health distress and hepatitis-specific limitations (recorded with the hepatitis-specific questions of the HQLQ). In each case, there is no hint of an added benefit of bulevirtide in comparison with BSC; an added benefit is therefore not proven.

Side effects

SAEs and severe AEs

There was no statistically significant difference between the treatment arms for the outcomes of SAEs and severe AEs. There is no hint of greater or lesser harm of bulevirtide in comparison with BSC; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

There were no discontinuations due to AEs during the course of the study. There is no hint of greater or lesser harm of bulevirtide in comparison with BSC for the outcome discontinuation due to AEs; greater or lesser harm is therefore not proven.

Symptomatic increase of bile salts

No suitable data were available for the outcome of symptomatic increase of bile salts (see Section I 3.2.1 for reasoning). There is no hint of greater or lesser harm of bulevirtide in comparison with BSC; greater or lesser harm is therefore not proven.

General disorders and administration site conditions (AEs)

A statistically significant difference to the disadvantage of bulevirtide in comparison with no treatment was shown for the outcome of general disorders and administration site conditions (AEs). There is a hint of greater harm of bulevirtide in comparison with BSC for this outcome.

Nervous system disorders (AEs)

A statistically significant difference to the disadvantage of bulevirtide in comparison with no treatment was shown for the outcome nervous system disorders (AEs). There is a hint of greater harm of bulevirtide in comparison with BSC for this outcome.

I 3.2.4 Subgroups and other effect modifiers

The following subgroup characteristics were taken into account in this benefit assessment:

- Sex (female versus male)
- Cirrhosis at baseline (yes versus no)

Age was also considered a relevant characteristic for a subgroup analysis. Since the cut-off values used by the company for age (< median / ≥ median) were not a meaningful cut-off value in terms of content, there were no suitable subgroup analyses for the characteristic of age.

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

The results are presented in Table 13.

Table 13: Subgroups (health-related quality of life) – RCT, direct comparison: bulevirtide vs. no treatment

Study Outcome Characteristic Subgroup	bulevirtide		No treatment		bulevirtide vs. no treatment	
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]	p-value ^a
MYR301						
HQLQ^b (SF-36, Mental Component Summary (MCS) – improvement at Week 48^c)						
Cirrhosis at baseline						
Yes	23	2 (8.7)	24	6 (25.0)	0.35 [0.08; 1.55]	0.153
No	26	11 (42.3)	27	2 (7.4)	5.71 [1.40; 23.33]	0.003
Total					Interaction:	0.008 ^d
a. Institute's calculation, unconditional exact test (CSZ method according to [25]). b. Consisting of the SF-36 and 15 additional hepatitis-specific questions. c. An increase in MCS by ≥ 9.6 points from baseline is considered a clinically relevant improvement (scale range: 5.8 to 69.9; determined using the 2009 norm sample [26]). d. Q test for heterogeneity. CI: confidence interval; CSZ: convexity, symmetry, z-score; HQLQ: Hepatitis Quality of Life Questionnaire; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; SF-36: Short Form 36						

Health-related quality of life

HQLQ (SF-36)

Mental Component Summary (MCS)

There was an effect modification for the characteristic cirrhosis at baseline for the MCS (recorded with the SF-36 of the HQLQ).

A statistically significant difference in favour of bulevirtide in comparison with no treatment was shown for patients without cirrhosis at baseline. There is a hint of an added benefit of bulevirtide in comparison with BSC for patients without cirrhosis at baseline.

No statistically significant difference between the treatment arms was shown for patients with cirrhosis at baseline. There is no hint of an added benefit of bulevirtide in comparison with BSC; an added benefit in this patient group is therefore not proven.

I 3.3 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the IQWiG General Methods [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

I 3.3.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was assessed based on the results presented in Section I 3.2 (see Table 14).

Table 14: Extent of added benefit at outcome level: bulevirtide vs. BSC (multipage table)

Outcome category Outcome Effect modifier Subgroup	bulevirtide vs. no treatment Proportion of events (%) Effect estimation [95% CI]; p-value Probability ^a	Derivation of extent ^b
Mortality		
All-cause mortality	0 vs. 0 RR: NC; p = NC	Lesser benefit not proven / added benefit not proven
Morbidity		
Liver-related events	0 vs. 0 RR: NC; p = NC	Lesser benefit not proven / added benefit not proven
Fatigue (FSS – improvement at Week 48)	40.8 vs. 25.5 RR: 1.60 [0.90; 2.85]; p = 0.121	Lesser benefit not proven / added benefit not proven
Health status (EQ-5D VAS – improvement at Week 48)	34.7 vs. 25.5 RR: 1.36 [0.74; 2.50]; p = 0.364	Lesser benefit not proven / added benefit not proven
Health-related quality of life		
HQLQ (SF-36 – improvement at Week 48)		
Physical Component Summary (PCS)	8.2 vs. 5.9 RR: 1.39 [0.33; 5.88]; p = 0.717	Lesser benefit not proven / added benefit not proven
Mental Component Summary (MCS)		
Cirrhosis at baseline		
Yes	8.7 vs. 25.0 RR: 0.35 [0.08; 1.55] p = 0.153	Lesser benefit not proven / added benefit not proven
No	42.3 vs. 7.4 RR: 5.71 [1.40; 23.33] RR: 0.18 [0.04; 0.71] ^c p = 0.003 Probability: hint	Outcome category: health-related quality of life CI _u < 0.75, risk ≥ 5% Added benefit, extent: major
HQLQ (hepatitis-specific questions – improvement at Week 48)		
Health distress	49.0 vs. 35.3 RR: 1.39 [0.87; 2.22]; p = 0.222	Lesser benefit not proven / added benefit not proven
Positive well-being	22.4 vs. 21.6 RR: 1.04 [0.50; 2.18]; p = 0.948	Lesser benefit not proven / added benefit not proven

Table 14: Extent of added benefit at outcome level: bulevirtide vs. BSC (multipage table)

Outcome category Outcome Effect modifier Subgroup	bulevirtide vs. no treatment Proportion of events (%) Effect estimation [95% CI]; p-value Probability ^a	Derivation of extent ^b
Hepatitis-specific health distress	57.1 vs. 45.1 RR: 1.27 [0.86; 1.87]; p = 0.250	Lesser benefit not proven / added benefit not proven
Hepatitis-specific limitations	32.7 vs. 15.7 RR: 2.08 [0.98; 4.42]; p = 0.057	Lesser benefit not proven / added benefit not proven
Side effects		
SAEs	4.1 vs. 2.0 RR: 2.08 [0.19; 22.23]; p = 0.598	Greater/lesser harm not proven
Severe AEs	10.2 vs. 7.8 RR: 1.30 [0.37; 4.56]; p = 0.771	Greater/lesser harm not proven
Discontinuation due to AEs	0 vs. 0 RR: NC; p = NC	Greater/lesser harm not proven
Symptomatic increase of bile salts	No suitable data ^d	Greater/lesser harm not proven
General disorders and administration site conditions (AEs)	30.6 vs. 3.9 RR: 7.81 [1.88; 32.37]; RR: 0.13 [0.03; 0.53] ^c p < 0.001 Probability: hint	Outcome category: non-serious/non-severe symptoms/late complications Cl _u < 0.80 Greater harm, extent: considerable
Nervous system disorders (AEs)	22.4 vs. 0 RR: 23.92 [1.45; 395.20]; RR: 0.04 [< 0.01; 0.69] ^c p < 0.001 Probability: hint	Outcome category: non-serious/non-severe symptoms/late complications Cl _u < 0.80 Greater harm, extent: considerable
a. Probability provided if there is a statistically significant and relevant effect. b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (Cl_u). c. Institute's calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit. d. See Section I 3.2.1 of this dossier assessment for reasoning.		
AE: adverse event; BSC: best supportive care; CI: confidence interval; Cl_u: upper limit of the confidence interval; FSS: Fatigue Severity Scale; HQLQ: Hepatitis Quality of Life Questionnaire; NC: not calculable; RR: relative risk; SF-36: Short Form 36; SAE: serious adverse event; VAS: visual analogue scale		

I 3.3.2 Overall conclusion on added benefit

Table 15 summarizes the results taken into account for the overall conclusion on the extent of the added benefit.

Table 15: Positive and negative effects from the assessment of bulevirtide in comparison with BSC

Positive effects	Negative effects
Health-related quality of life ▪ HQLQ (SF-36, Mental Component Summary [MCS]) ▫ Cirrhosis at baseline (no) Hint of an added benefit – extent: major	
	Non-serious / non-severe side effects ▪ General disorders and administration site conditions: hint of greater harm – extent: considerable ▪ Nervous system disorders: hint of greater harm – extent: considerable
AE: adverse event; BSC: best supportive care; HQLQ: Hepatitis Quality of Life Questionnaire; SF-36: Short Form 36	

For research question 1 of this assessment, both positive and negative effects were shown for bulevirtide in comparison with BSC.

On the positive effects side, in the category of health-related quality of life, there is a hint of an added benefit with the extent ‘major’ for MCS for patients without cirrhosis at baseline. This positive effect was only shown on this scale of the generic questionnaire, but not on the disease-specific scales on health-related quality of life. Therefore, given the available data, the positive effect in the outcome MCS for patients without liver cirrhosis at baseline was not assessed as sufficient to justify a derivation of the added benefit separately by subgroup.

On the side of negative effects, in the category non-serious / non-severe side effects for the specific AEs general disorders and administration site conditions and nervous system disorders, there is a hint of greater harm with considerable extent. In the overall view of the available results, these negative effects in the specific AEs are not sufficient to justify a lesser benefit.

In summary, there is no hint of an added benefit of bulevirtide in comparison with the ACT BSC for plasma (or serum) HDV-RNA positive adult patients with chronic HDV infection with compensated liver disease.

The assessment described above differs from that of the company, which derived an indication of considerable added benefit.

I 4 Research question 2: children and adolescents (3 to < 18 years) with chronic HDV infection

I 4.1 Information retrieval and study pool

The study pool for the assessment was compiled on the basis of the following information:

Sources used by the company in the dossier:

- Study list on bulevirtide (status: 11 July 2025)
- Bibliographical literature search on bulevirtide (last search on 11 July 2025)
- Search of trial registries / trial results databases for studies on bulevirtide (last search on 11 July 2025)
- Search on the G-BA website for bulevirtide (last search on 11 July 2025)

To check the completeness of the study pool:

- Search of trial registries for studies on bulevirtide (last search on 15 September 2025); for search strategies, see I Appendix A of the full dossier assessment

Consistent with the findings of the company, the review of the completeness of the study pool did not produce any RCTs for this research question.

Due to the lack of RCTs for children and adolescents, the company conducted an information retrieval for adult patients in the given therapeutic indication. It did not conduct an information retrieval for further investigations in children and adolescents. For the assessment of the added benefit, the company sought to transfer study results from adult patients in the therapeutic indication to the paediatric population of this research question. As for research question 1, the company used study MYR301 and additionally study MYR202 for this purpose (see Section I 3.1).

The data presented by the company were not suitable for drawing conclusions on the added benefit of bulevirtide in comparison with BSC for the population of the research question at hand, i.e. children and adolescents (3 to < 18 years) with chronic HDV infection. The studies presented are described in Section I 3.1 of this benefit assessment. This is justified below.

Transfer of results from adult patients from the RCT MYR301 to the target population not possible

The company transferred the results from the RCT MYR301 (see Section I 3.1.1) and additionally MYR202 [3] with exclusively adult study participants to the paediatric population. It justified this transfer with what it considered to be comparability of the disease profile, the mechanism of action and the clinical response under interferon therapy according to various

criteria of the EMA [27]. The company added that the MYR301 study had also been used by the EMA for an evidence transfer from the adult to the paediatric population as part of the marketing authorization procedure for the paediatric population.

The company's approach of transferring study results from adult patients to the population of the given research question would be plausible in view of the lack of randomized comparative studies in paediatric patients. For the source population of adult patients in the therapeutic indication, the company conducted an information retrieval for RCTs. However, it did not conduct an information retrieval to identify all potentially relevant further investigations on the intervention and the ACT in the target population of children and adolescents. Irrespective of the missing information retrieval, the company did not present any data on the target population of children and adolescents. There were therefore no studies or clinical data for children and adolescents under the age of 18 to support the transferability of the results from adult to paediatric patients. EMA's extension of the marketing authorization for the paediatric population was also based purely on modelling for children and adolescents based solely on the complete extrapolation of pharmacokinetic/pharmacodynamic data from adults. Notwithstanding this, this benefit assessment did not determine any added benefit in the adult population based on the MYR301 study that could be transferred to children and adolescents (see Section I 3.3.2).

I 4.2 Results on added benefit

No suitable data were available for the assessment of the added benefit of bulevirtide in comparison with the ACT for plasma (or serum) HDV-RNA positive children and adolescents 3 to < 18 years of age weighing at least 10 kg with chronic HDV infection with compensated liver disease. There is no hint of an added benefit of bulevirtide in comparison with the ACT; an added benefit is therefore not proven.

I 4.3 Probability and extent of added benefit

In its dossier, the company did not present any suitable data for the assessment of the added benefit of bulevirtide in comparison with the ACT for plasma (or serum) HDV-RNA positive children and adolescents 3 to < 18 years of age weighing at least 10 kg with chronic HDV infection with compensated liver disease. An added benefit of bulevirtide versus the ACT is therefore not proven for research question 2.

The assessment described above departs from that by the company, which derived a hint of considerable added benefit for the patients in this research question.

I 5 Probability and extent of added benefit – summary

Table 16: Bulevirtide – probability and extent of added benefit

Research question	Therapeutic indication	ACT ^a	Probability and extent of added benefit
1	Adults with chronic HDV infection with compensated liver disease	Best supportive care ^{b, c}	Added benefit not proven
2	Children and adolescents 3 to < 18 years of age weighing at least 10 kg with chronic HDV infection with compensated liver disease	Best supportive care ^{b, c}	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, appropriate treatment of the underlying HBV infection corresponding to the generally accepted current state of medical knowledge is assumed; according to the S3 guideline, the use of PEG-IFN for the treatment of HBV infection should be considered in patients with chronic HBV/HDV co-infection. PEG-IFN is not authorized for the treatment of HDV infection.
c. Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; HBV: hepatitis B virus; HDV: hepatitis delta virus; PEG-IFN: peginterferon alfa-2a

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

Supplementary note

The result of the assessment deviates from the result of the G-BA's assessment conducted in the context of the market launch in 2020, where the G-BA had determined a non-quantifiable added benefit of bulevirtide for plasma (or serum) HDV-RNA positive adults with chronic HDV infection with compensated liver disease. However, in the G-BA's assessment the added benefit was considered proven by the marketing authorization, regardless of the underlying data, due to the special situation for orphan drugs.

I 6 References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 7.0 [online]. 2023 [Accessed: 02.09.2024]. URL: https://www.iqwig.de/methoden/allgemeine-methoden_version-7-0.pdf.
2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. *Biom J* 2016; 58(1): 43-58. <https://doi.org/10.1002/bimj.201300274>.
3. Wedemeyer H, Schoneweis K, Bogomolov P et al. Safety and efficacy of bulevirtide in combination with tenofovir disoproxil fumarate in patients with hepatitis B virus and hepatitis D virus coinfection (MYR202): a multicentre, randomised, parallel-group, open-label, phase 2 trial. *Lancet Infect Dis* 2023; 23(1): 117-129. [https://doi.org/10.1016/S1473-3099\(22\)00318-8](https://doi.org/10.1016/S1473-3099(22)00318-8).
4. Gemeinsamer Bundesausschuss. Nutzenbewertungsverfahren zum Wirkstoff Bulevirtid (Chronische Hepatitis-Delta-Virus (HDV)-Infektion, HDV-RNA-positiv) [online]. 2020 [Accessed: 16.09.2025]. URL: <https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/582/>.
5. European Medicines Agency. Hepcludex; Assessment report [online]. 2020 [Accessed: 02.09.2025]. URL: https://www.ema.europa.eu/en/documents/assessment-report/hepcludex-epar-public-assessment-report_en.pdf.
6. Gilead Sciences. A Multicenter, Open-label, Randomized Phase 3 Clinical Study to Assess Efficacy and Safety of Bulevirtide in Patients with Chronic Hepatitis Delta; study MYR301; Clinical Study Report [unpublished]. 2022.
7. Gilead Sciences. A Multicenter, Open-label, Randomized Phase 3 Clinical Study to Assess Efficacy and Safety of Bulevirtide in Patients with Chronic Hepatitis Delta [online]. [Accessed: 03.11.2025]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2019-001213-17.
8. Gilead Sciences. Study to Assess Efficacy and Safety of Bulevirtide in Participants With Chronic Hepatitis Delta (CHD) [online]. 2025 [Accessed: 10.11.2025]. URL: <https://clinicaltrials.gov/study/NCT03852719>.
9. Wedemeyer H, Aleman S, Brunetto MR et al. A Phase 3, Randomized Trial of Bulevirtide in Chronic Hepatitis D. *N Engl J Med* 2023; 389(1): 22-32. <https://doi.org/10.1056/NEJMoa2213429>.

10. Gilead. HEPCLUDEX 2 mg Pulver zur Herstellung einer Injektionslösung [online]. 09.2025 [Accessed: 10.11.2025]. URL: <https://www.fachinfo.de>.
11. Cornberg M, Sandmann L, Protzer U et al. S3-Leitlinie der Deutschen Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (DGVS) zur Prophylaxe, Diagnostik und Therapie der Hepatitis-B-Virusinfektion. Z Gastroenterol 2021; 59(7): 691-776. <https://doi.org/10.1055/a-1498-2512>.
12. European Association for the Study of the L. EASL Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2025; 83(2): 502-583. <https://doi.org/10.1016/j.jhep.2025.03.018>.
13. Terrault NA, Lok ASF, McMahon BJ et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 2018; 67(4): 1560-1599. <https://doi.org/10.1002/hep.29800>.
14. Sandmann L, Berg T, Deterding K et al. Addendum „Antivirale Therapie der chronischen Hepatitis-D-Virusinfektion“ zur S3-Leitlinie „Prophylaxe, Diagnostik und Therapie der Hepatitis-B-Virusinfektion“ der Deutschen Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (DGVS). Z Gastroenterol 2023; 61(12): 1635-1653. <https://doi.org/10.1055/a-2181-3046>.
15. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Boceprevir – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2011 [Accessed: 03.11.2025]. URL: https://www.iqwig.de/download/a11-17_boceprevir_nutzenbewertung_gemaess_35a_sgb_v.pdf.
16. Singal AG, Volk ML, Jensen D et al. A sustained viral response is associated with reduced liver-related morbidity and mortality in patients with hepatitis C virus. Clin Gastroenterol Hepatol 2010; 8(3): 280-288.e1. <https://doi.org/10.1016/j.cgh.2009.11.018>.
17. Asselah T, Rizzetto M. Hepatitis D Virus Infection. N Engl J Med 2023; 389(1): 58-70. <https://doi.org/10.1056/NEJMra2212151>.
18. Ghany MG, Buti M, Lampertico P et al. 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 2023; 78(5): 1654-1673. <https://doi.org/10.1097/HEP.0000000000000431>.
19. Ghany MG. A Glimmer of Hope for an Orphan Disease. N Engl J Med 2023; 389(1): 81-82. <https://doi.org/10.1056/NEJMe2304147>.
20. Da BL. Clinical trials in hepatitis D virus: Measuring success. Hepatology 2023; 77(6): 2147-2157. <https://doi.org/10.1002/hep.32732>.

21. Food and Drug Administration. Chronic Hepatitis D Virus Infection: Developing Drugs for Treatment;. Guidance for Industry; Draft Guidance [online]. 2019 [Accessed: 07.10.2025]. URL: <https://www.fda.gov/media/132137/download>.
22. Krupp LB, LaRocca NG, Muir-Nash J et al. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol 1989; 46(10): 1121-1123. <https://doi.org/10.1001/archneur.1989.00520460115022>.
23. Bayliss MS, Gandek B, Bungay KM et al. A questionnaire to assess the generic and disease-specific health outcomes of patients with chronic hepatitis C. Qual Life Res 1998; 7(1): 39-55. <https://doi.org/10.1023/a:1008884805251>.
24. Lampertico P, Chohan A, Elwick H et al. Exploring the patient experience of chronic hepatitis D (CHD) and assessment of content validity of the Hepatitis Quality of Life Questionnaire and (HQLQv2) and the Fatigue Severity Scale (FSS). J Patient Rep Outcomes 2025; 9(1): 84. <https://doi.org/10.1186/s41687-025-00903-3>.
25. Martín Andrés A, Silva Mato A. Choosing the optimal unconditioned test for comparing two independent proportions. Computat Stat Data Anal 1994; 17(5): 555-574. [https://doi.org/10.1016/0167-9473\(94\)90148-1](https://doi.org/10.1016/0167-9473(94)90148-1).
26. Maruish ME. User's manual for the SF-36v2 Health Survey (3rd edition). Lincoln, RI: Quality Metric Incorporated. 2011.
27. European Medicines Agency. Reflection paper on the use of extrapolation in the development of medicines for paediatrics [online]. 2018 [Accessed: 06.10.2025]. URL: https://www.ema.europa.eu/en/documents/scientific-guideline/adopted-reflection-paper-use-extrapolation-development-medicines-paediatrics-revision-1_en.pdf.

The full report (German version) is published at
<https://www.iqwiq.de/en/projects/a25-113.html>.