EMA/763187/2022
Committee for Medicinal Products for Human Use (CHMP)

Type II variation assessment report

Procedure No. EMEA/H/C/004854/II/0019

Invented name: Hepcludex

International non-proprietary name: bulevirtide

Marketing authorisation holder (MAH): Gilead Sciences Ireland Unlimited Company

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted

Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure	17 Oct 2022	17 Oct 2022
☐	CHMP Rapporteur Assessment Report	21 Nov 2022	21 Nov 2022
☐	CHMP members comments	05 Dec 2022	25 Nov 2022
☐	Updated CHMP Rapporteur Assessment Report	08 Dec 2022	08 Dec 2022
☐	Request for Supplementary Information (RSI)	15 Dec 2022	15 Dec 2022
☐	Submission deadline	23 Feb 2023	23 Feb 2023
☐	Re-start date	26 Feb 2023	26 Feb 2023
☐	CHMP Rapporteur Assessment Report	03 Apr 2023	30 Mar 2023
☐	CHMP members comments	17 Apr 2023	17 Apr 2023
☐	Updated CHMP Rapporteur Assessment Report	20 Apr 2023	N/A
☒	Opinion	26 Apr 2023	26 Apr 2023

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Gilead Sciences Ireland Unlimited Company submitted to the European Medicines Agency on 2 September 2022 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

Update of sections 4.8 and 5.1 of the SmPC in order to update the list of adverse drug reactions (ADRs) and efficacy information based on interim results from study MYR301 listed as a Specific Obligation in the Annex II of the Product Information; this is a Multicenter, Open-label, Randomized Phase III Clinical Study to Assess Efficacy and Safety of Bulevirtide in Patients with Chronic Hepatitis Delta. Consequently, the MAH proposes a switch from conditional marketing authorisation to full marketing authorisation given the fulfilment of the SOB. The Package Leaflet is updated accordingly.
In addition, the MAH took the opportunity to implement editorial changes in the SmPC.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

2. Overall conclusion and impact on the benefit/risk balance

Chronic HDV infection with active hepatitis, is indicated by a positive HDV RNA and ALT elevation. Approximately 5% of individuals infected with hepatitis B virus (HBV) are coinfected with hepatitis D virus (HDV). Chronic HBV/HDV coinfection is associated with an unfavourable outcome, with many patients developing liver cirrhosis, liver failure and eventually hepatocellular carcinoma within 5–10 years.

Currently there is no therapy specific for HDV approved in the EU other than bulevertide (BLV). Hepcludex is indicated for "the treatment of chronic hepatitis delta virus (HDV) infection in plasma (or serum) HDV-RNA positive adult patients with compensated liver disease."

The scope of this variation is the submission of interim results at 48 weeks from study MYR301, which was the key specific obligation for the CMA of BLV. This investigates the efficacy and safety of 2 or 10 mg BLV, compared to delayed treatment over 96 weeks. MYR301 was designed as a multicenter, parallel-group open-label, randomized phase III clinical trial. 150 participants received the drug with 50/49/51 patients in the arms delayed treatment/BLV 2 mg/ BLV 10 mg.

In MYR301, the primary efficacy end point (undetectable HDV RNA or decrease in HDV RNA by ≥ 2 $\log_{10}$ IU/mL from baseline and ALT normalization at 48 weeks) was achieved in 42.9% in 2 mg BLV treatment group and in 48.0% in the 10 mg group. Results of treatment were significantly higher compared to the delayed treatment (2%).

The key secondary endpoint "the proportion of participants with undetectable HDV RNA" were 12.2% and 20.0 % in the 2 mg and 10 mg BLV treatment groups respectively, at 48 weeks. None of the patients in the delayed treatment group achieved the key secondary endpoint. Furthermore, considerably higher rates of ALT normalization were reached with 2mg (51.0%) and 10 mg (56.0%) compared to delayed treatment (11.8%) with only numerical differences seen between 2mg and 10mg BLV treatment.

Overall, BLV is well tolerated, with asymptomatic bile acid increases (18.8% and 27.7% with 2 and 10 mg,

respectively, pooled safety data set) and injection site reactions (16.3%; 2 mg BLV, 30.0%; 10 mg BLV) being the most common events. SAEs frequencies were low (2-4%) in treatment and delayed treatment arms. No deaths occurred. Frequently occurring AEs include eosinophilia, fatigue, injection site reactions, headache and arthralgia at 48 weeks. The safety database is overall considered small, which precludes certain conclusions regarding rare AEs**.** No safety concerns were identified**.**

The presented data confirmed the benefits assumed at the time of the Conditional Marketing Authorisation. Moreover, no clinically relevant differences were seen between 2mg and 10mg, supporting the initial dose selection of 2 mg.

No new safety concerns were definitely identified, and it is not expected that the remaining outstanding data in MYR301 will alter the benefit risk profile of Hepcludex. The SOB has been reclassified as a Category 3 study in the RMP and removed from Annex II. The Marketing Authorisation Holder (MAH) has updated the SmPC 5.1 adding primary endpoints results from week 48. Moreover, it has shortened the previously accepted presentation of data from the phase II programme, as requested.

The MAH has updated the frequencies of pruritus and injection site reactions from common to very common, which is endorsed based on the presented data.

Balance of benefits and risks

Based on the review of all available data, the CHMP considers that the benefit-risk balance of Hepcludex outweigh remains positive.

Scientific grounds for recommending the granting of a marketing authorisation not subject to specific obligations

The MAH provided within this variation their position that comprehensive data are available about the safety and efficacy of Hepcludex and supporting the favourable benefit/risk profile of in all approved populations, as the submission of this variation application contains the data outstanding from the last remaining specific obligation (SOB) as follows:

Description	**Due date**
MYR 301 - A Multicentre, Open-label, Randomized Phase 3 Clinical Study to Assess Efficacy and Safety of Bulevirtide in Patients with Chronic Hepatitis Delta	28 February 2025

The MAH has therefore requested to take the opportunity of the present renewal of conditional marketing authorisation to remove the submission of the MYR 301 from the list of specific obligations and to adopt an opinion recommending the granting of a marketing authorisation in accordance with Article 14(1) of Regulation (EC) No 726/2004 ('marketing authorisation not subject to specific obligations').

During the period covered by this annual renewal, new data on the current SOB have been generated. The clinical safety profile, as well as the efficacy of this product is considered comprehensively characterised and supportive of a positive benefit-risk balance. The SOB (MYR 301) may therefore be reclassified as category 3 studies in the RMP and deleted from Annex II.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to	Type II	I, II and

Variation requested		Type	Annexes affected
	new quality, preclinical, clinical or pharmacovigilance data		IIIB

Update of sections 4.8 and 5.1 of the SmPC in order to update the list of adverse drug reactions (ADRs) and efficacy information based on interim results from study MYR301 listed as a Specific Obligation in the Annex II of the Product Information; this is a Multicenter, Open-label, Randomized Phase III Clinical Study to Assess Efficacy and Safety of Bulevirtide in Patients with Chronic Hepatitis Delta. As a result of this variation, the SmPC, Annex II and PL are also updated to reflect the completion of the specific obligation and the CHMP recommendation to grant a marketing authorisation no longer subject to specific obligations.
In addition, the MAH took the opportunity to implement editorial changes in the SmPC. The Package Leaflet is updated accordingly. Version 4.0 of the RMP has also been approved (Study MYR301 was reclassified from a Category 2 to a Category 3 study).

is recommended for approval.

The CHMP, having considered the application as set out in the appended assessment report and having reviewed the data submitted by the marketing authorisation holder including the evidence concerning compliance with specific obligations, is of the opinion that the risk-benefit balance of the above mentioned medicinal product remains favourable, that all specific obligations laid down in Annex II have been fulfilled and that comprehensive data supports a favourable benefit-risk balance of the above mentioned medicinal product. Therefore, pursuant to Article 14-a(8) of Regulation (EC) No 726/2004, the CHMP recommends by consensus the granting of a marketing authorisation in accordance with Article 14(1) of Regulation (EC) No 726/2004 for Hepcludex (bulevirtide).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I, II and IIIB are recommended.

As a result of this variation, it is recommended that the following obligation is deleted from the Annex II to the Opinion:

Description	Due date
MYR 301 - A Multicentre, Open-label, Randomized Phase 3 Clinical Study to Assess Efficacy and Safety of Bulevirtide in Patients with Chronic Hepatitis Delta	28 February 2025

PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Annex: Rapporteur’s assessment comments on the type II variation

4. Introduction

Bulevirtide (2 mg given subcutaneously once daily) is conditionally approved for the treatment of chronic hepatitis delta virus (HDV) infection in plasma (or serum) HDV-RNA positive adult patients with compensated liver disease under the brand name Hepcludex in the European Union (EU) and other countries within Europe and is fully approved as Myrcludex B for the treatment of CHD in adults in the Russian Federation.

HDV is a satellite virus of HBV which requires the presence of HBV for its replication. Chronic HBV/HDV infection is associated with an increased risk of liver cirrhosis, hepatic decompensation, and hepatocellular carcinoma.

On 31 July 2020, the European Commission granted a Conditional Marketing Authorization (CMA) for Hepcludex. Upon approval of the Hepcludex CMA, there was 1 Specific Obligation (SOB) to fulfill (Study MYR301).

Study MYR301 is the key confirmatory study for BLV. It is a Phase 3, randomized, open-label, multicenter, parallel-group study that evaluates the efficacy and safety of BLV administered subcutaneously (SC) at a dose of 2 mg or 10 mg once daily for treatment of CHD in comparison with delayed treatment.

Eligible participants received immediate treatment with BLV 2 mg/day or BLV 10 mg/day, each given for 144 weeks, or delayed treatment with BLV 10 mg/day after an observational period of 48 weeks (delayed treatment), after which they were treated for 96 weeks.

Included in this submission are updated clinical efficacy and safety data (Week 48) from the ongoing Study MYR301 (SOB) that support the use of BLV for the treatment of CHD in adults with compensated liver disease. Supportive pooled safety data analysis from Week 48 of the Phase 2 Study MYR203 and the Phase 3 Study MYR301 are also included, where appropriate, to support the proposed presentation of adverse drug reactions (ADRs) and their frequencies in the EU summary of product characteristics (SmPC) updates. This m2.5 addresses the benefit-risk assessment generated for the SOB and presents data up to Week 48 from the ongoing Study MYR301. Included in this submission are the relevant clinical study reports (CSRs):

- MYR301 Week 24 Interim CSR
- MYR301 Week 48 Interim CSR (Revision)

5. Clinical Pharmacology aspects

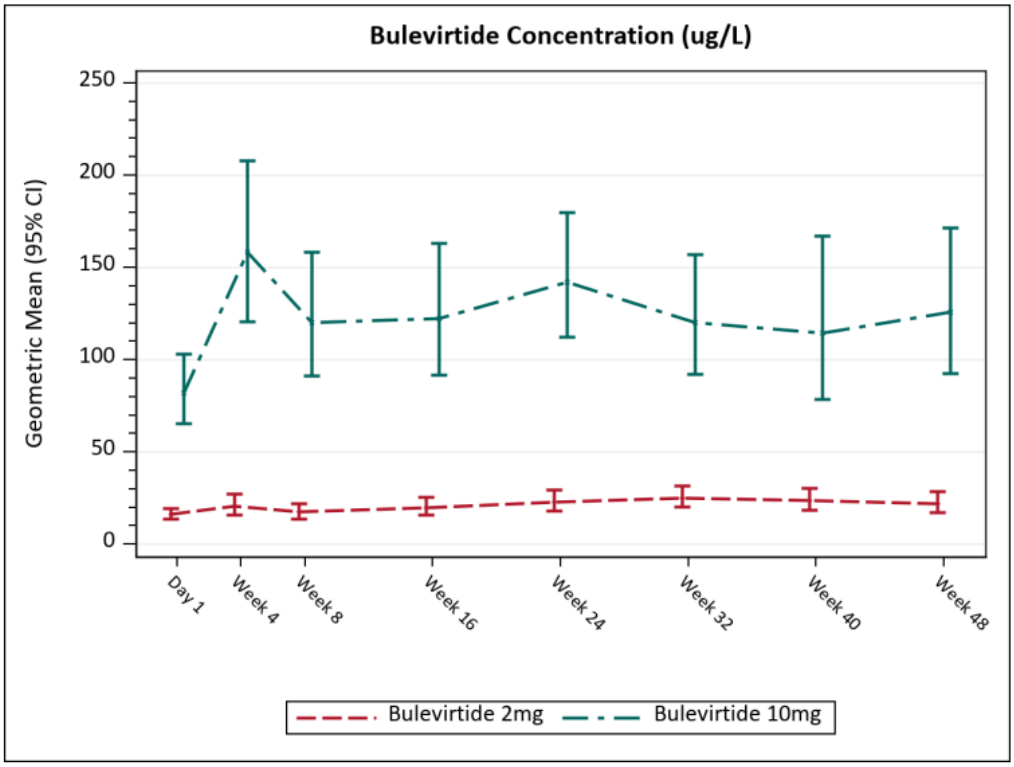
5.1 Pharmacokinetics

Blood sampling was performed at the randomization/baseline visit (Visit 1) and at all treatment visits after the start of BLV therapy. Sampling was done 1 hour ± 15 minutes after BLV SC injection. During the first 48 weeks, PK samples were collected only for the BLV 2 mg and BLV 10 mg groups. Frozen samples were sent to the central laboratory for analysis.

At Day 1, measured 1 hour ± 15 min after SC injection of BLV, the geometric mean (%CV) concentrations of BLV were 16.2 µg/L (66.8%) in participants treated BLV 2 mg and 82.0 µg/L (98.9%) in participants treated with BLV 10 mg. In the BLV 2 mg group, similar plasma concentrations were observed from Week 4 to Week 48, with geometric mean plasma concentrations of 20.8 µg/L and 22.2 µg/L at Week 4 and Week 48, respectively. In the BLV 10 mg group, the geometric mean plasma concentrations were 158.2 µg/L and

126.1 µg/L at Week 4 and Week 48, respectively. Overall, this indicated that steady state is achieved by Week 4, with no further increase in plasma concentrations at later time points. High variability in BLV plasma concentrations was observed in BLV dose groups (2 mg and 10 mg), with %CV ranging from 64% to 152% across time points.

Figure 1. MYR301: Geometric mean (95% CI) plasma concentrations of bulevirtide during the first 48 weeks of treatment (safety analysis set).



a Pharmacokinetic samples collected 1 hour ± 15 minutes after bulevirtide injection on Visit Day.
Source: Section 15.1, Figure 14.5-1 and Table 14.5-1

5.2 Assessor's Discussion – pharmacokinetics

The MAH has only collected sparse pharmacokinetic (PK) data within the present Phase III study MYR301. PK samples were taken at all treatment visits at a single time point of 1 hour ± 15 minutes after BLV sc injection. BLV concentrations measured in the present study MYR301, correspond approximately to its Cmax values. Plasma concentrations measured after 2 mg dose were lower than after 10 mg dose, as expected. Geometric mean concentrations measured at week 48 after the dose of 2 mg and 10 mg were 22.2 µg/L and 126.1 µg/L, respectively. Concentrations measured at Week 4 were generally similar to Week 48 concentrations (for both dose levels), thus implying a steady-state condition reached by Week 4. Overall, a relatively high variability in BLV plasma concentrations was observed at both dose levels. The MAH is not proposing any SmPC updates related to PK as a part of the current Variation II procedure, which is considered acceptable.

7. Clinical Efficacy aspects

7.1. Methods – analysis of data submitted

Study Participants and Treatments

This ongoing Phase 3, randomized, open-label, parallel-group, multicenter study compares the efficacy and safety of BLV administered as delayed treatment (10 mg subcutaneous once daily after 48 weeks) versus immediate treatment (2 mg or 10 mg subcutaneous once daily) for the treatment of CHD in participants with compensated cirrhosis or without cirrhosis.

Participants were randomized in a 1:1:1 ratio to 1 of the following 3 treatment groups for a treatment period of 144 weeks:

- Treatment Group A: Delayed treatment with BLV 10 mg/day for 96 weeks after an observational period of 48 weeks with an additional follow-up period of 96 weeks
- Treatment Group B: Immediate treatment with BLV 2 mg/day for 144 weeks with a further follow-up period of 96 weeks
- Treatment Group C: Immediate treatment with BLV 10 mg/day for 144 weeks with a further follow-up period of 96 weeks

Randomization was stratified for liver cirrhosis status (no/yes).

Key inclusion criteria: Eligible participants were males or females aged 18 to 65 years with positive serum anti-HDV antibody results or PCR results for serum/plasma HDV RNA for at least 6 months before screening, positive PCR results for serum/plasma HDV RNA at screening, and ALT level > 1 × ULN, but less than 10 × ULN. Participants with controlled human immunodeficiency virus coinfection were allowed as well as participants with HCV antibodies, if screening HCV RNA test was negative.

Key exclusion criteria: Child-Pugh hepatic insufficiency score over 7 points; participants with current or previous (within the past 2 years) decompensated liver disease; one or more additional known primary or secondary causes of liver disease, other than hepatitis B; use of interferons (IFN) within 6 months before screening.

A total of 183 participants were screened. Of the 183 participants screened, 150 were randomized (delayed treatment group: 51 participants; BLV 2 mg treatment group: 49 participants; BLV 10 mg treatment group: 50 participants), and 99 participants received at least 1 dose of study drug (BLV 2 mg treatment group: 49 participants; BLV 10 mg treatment group: 50 participants); 51 participants were randomized to the delayed treatment group and as such did not receive study drug before their data cut-off date for the Week 48 primary end point analysis.

Prior and Concomitant Therapy

Participants who had ongoing treatment with nucleoside/nucleotide analogues for CHB were allowed to continue their treatment as prescribed on screening and during study participation. For participants with no ongoing treatment with nucleoside/nucleotide analogues for CHB, treatment was to be initiated at the baseline visit or later in the study if indicated in accordance with the current EASL/AASLD treatment guidelines (current as of November 2018). Anti-HBV treatment was to be started if one of following conditions was met:

- (HBV DNA > 2000 IU/mL and ALT > ULN) or (HBV DNA > 2000 IU/mL and at least moderate liver necroinflammation or fibrosis) or (HBV DNA > 2000 IU/mL and ALT > ULN and at least moderate liver necroinflammation or fibrosis)
- Liver cirrhosis with any detectable HBV DNA level

- Participants with HBV DNA > 20,000 IU/mL and ALT > 2 × ULN were to start treatment regardless of the degree of fibrosis
- Family history of cirrhosis or hepatocellular carcinoma
- Presence of extrahepatic manifestations

Study MYR301 Key dates

Event	Date
First Participant Screened	17 April 2019
First Participant Enrolled/Randomized	08 May 2019
Last Participant Enrolled/Randomized	23 December 2019
Last Participant Last Visit for The Primary End Point	26 November 2020
Last Participant Last Visit for This Report	26 November 2020
Database Finalization for This Interim Report	16 April 2021

Endpoints

The primary efficacy end point for Study MYR301 was the proportion of participants achieving combined response at Week 48. Combined response was defined as fulfilment of 2 conditions simultaneously: undetectable HDV RNA (HDV RNA < limit of detection [LOD]) or decrease in HDV RNA by ≥ 2 $\log_{10}$ IU/mL from baseline, and ALT normalization.

The key secondary efficacy end point was the proportion of participants receiving BLV treatment with undetectable HDV RNA at Week 48.

Other secondary efficacy endpoints included the following:
- Proportion of participants with ALT normalization at Week 48
- Change from baseline at Week 48 in liver stiffness as measured by elastography
- The proportion of participants with HDV RNA decrease by ≥ 2 $\log_{10}$ IU/mL from baseline or undetectable HDV RNA (viral response) at Week 48.

Exploratory efficacy end points included the following:
- Liver fibrosis and changes in histological activity at Week 48 (for participants who consented to undergo a liver biopsy at baseline and Week 48)
- Serological analyses at Week 48:
  - HBsAg loss with or without seroconversion
  - HBsAg response (defined as HBsAg decrease by > 1 $\log_{10}$ IU/mL)
  - Change from baseline in HBsAg levels ($\log_{10}$ scale)
  - HBeAg loss with or without seroconversion
- Change from baseline in HBV DNA levels ($\log_{10}$ scale) at Week 48
- Incidence of liver-related events from baseline through Week 48
- Quality of life questionnaires (assessed at Week 48)

Statistical analyses

Full Analysis Set

The Full Analysis Set (FAS) included all participants either randomized to the delayed treatment group or randomized to BLV and received BLV at least once after randomization. Analysis of the FAS was based on the planned treatment (ie, participants were analyzed "as randomized").

Per Protocol Analysis Set

The Per Protocol (PP) Analysis Set for the Week 48 primary end point analysis was defined as all participants in the FAS for whom no PD judged as having an impact on the primary efficacy analysis was reported or identified.

Safety Analysis Set

The Safety Analysis Set included all participants randomized to the delayed treatment group or randomized to BLV and received BLV at least once after randomization. Analysis on the safety population was based on the actual treatment (ie, participants were analyzed "as treated").

Analyses

An interim analysis was performed on the primary end point at Week 24. Therefore, to account for the repeated analysis and also maintain the nominal 2-sided significance level of 0.05, this level was to be split among the interim (Week 24) and primary end point analysis (Week 48), with an allocation of 0.01 to interim and 0.04 to the main analysis.

Multiple group comparisons for the primary end point and the inclusion of a main secondary end point were to be handled with a hierarchical testing procedure. All other analyses were to be considered exploratory and no adjustment for multiple testing was performed. This includes the liver stiffness parameter.

The expected response rates at Week 48 for the BLV 2 mg and 10 mg doses were at least 45%. The conservative expectation for the delayed treatment response rates was 8% or less. These assumptions were based on results from the preceding Phase 2 study (Study MYR202). With a sample size of 47 participants per treatment group, a Fisher's exact test with a 0.04 2-sided significance level had 97.8% power to detect this difference between the BLV 10 mg and the delayed treatment proportions and between the BLV 2 mg and the delayed treatment proportions. The power to reject both null hypotheses simultaneously was 95.6%. This sample size was slightly increased to 50 participants per treatment group to account for a few potential early withdrawals before exposure. Hence, 150 participants were planned to be randomized.

Resistance analysis

Resistance analysis was performed on participants who experienced on-treatment virologic breakthrough or HDV RNA decline < 1 log10 IU/mL (non-responders) at Week 48.

Study Conduct

Following finalization of the original Week 48 CSR dated 18 January 2022, virologic sample switches were identified for some participants in the study, which impacted virology results for some participants. Subsequently, an assessment of the impact on the efficacy endpoints related to HDV RNA results was promptly conducted. Upon completion of the assessment, the MAH identified 14 affected HDV RNA samples from 10 participants. Protocol deviations relating to sample switches were only considered major if they impacted key time points (e.g., baseline or Week 48). The 5 major PDs identified from this assessment were categorized as "H – Laboratory Procedure."

The issue of sample switches was reflected in HDV RNA profiles over 48 weeks. Laboratory kits used for the collection and storage of HDV RNA samples also contained sample tubes that were used for additional analyses including: HBV and HDV virology (ie, plasma HBV DNA, HBsAg and anti-HBsAg antibody, HBeAg and antibody against hepatitis B e antigen, HBV and HDV genotype), immunogenicity (ie, ADA), sparse

PK samples, and samples for HBV and HDV sequencing and HDV phenotyping and for NTCP polymorphism sequencing (baseline only).

The procedures for collection and processing of safety samples were separate from the collection and processing procedures for efficacy samples. ALT levels were determined in real time as a component of routine safety monitoring, and as such, these samples were processed differently than virologic (efficacy) samples.

7.2 Results

Study disposition

A total of 150 participants were randomized (delayed treatment group: 51 participants; BLV 2 mg treatment group: 49 participants; BLV 10 mg treatment group: 50 participants), and 99 participants received at least 1 dose of study drug (BLV 2 mg treatment group: 49 participants; BLV 10 mg treatment group: 50 participants); 51 participants were randomized to the delayed treatment group and as such did not receive study drug before their data cutoff date for the Week 48 primary end point analysis

Of the 99 participants randomized and treated with BLV at 16 sites in 4 countries: 56 in Russia, 20 in Germany, 17 in Italy, and 6 in Sweden, 4 participants discontinued the study prior to the Week 48 data cutoff date.

Demographics

Table 1 MYR301: Demographic and Baseline Characteristics (Full Analysis Set)

Characteristic	Delayed Treatment (N = 51)	BLV 2 mg (N = 49)	BLV 10 mg (N = 50)	Total (N = 150)
Sex (n, %)				
Male	26 (51.0%)	30 (61.2%)	30 (60.0%)	86 (57.3%)
Female	25 (49.0%)	19 (38.8%)	20 (40.0%)	64 (42.7%)
Age (Years)				
Mean (SD)	40.5 (7.5)	43.6 (9.0)	41.3 (8.5)	41.8 (8.4)
Q1, Q3	35.0, 45.0	39.0, 49.0	35.0, 46.0	36.0, 47.0
Min, Max	27, 61	19, 62	22, 60	19, 62
Median (IQR)	40.0 (10.0)	43.0 (10.0)	40.0 (11.0)	41.0 (11.0)
Race (n, %)				
White	40 (78.4%)	41 (83.7%)	43 (86.0%)	124 (82.7%)
Black or African American	0	0	1 (2.0%)	1 (0.7%)
Asian	11 (21.6%)	8 (16.3%)	6 (12.0%)	25 (16.7%)
BMI (kg/m^2)				
Mean (SD)	25.26 (3.86)	24.40 (3.09)	25.09 (3.64)	24.92 (3.55)
Q1, Q3	22.36, 27.90	22.37, 26.67	22.60, 27.22	22.40, 27.04
Min, Max	18.5, 34.8	19.5, 31.4	17.6, 35.9	17.6, 35.9
Median (IQR)	25.14 (5.54)	24.22 (4.30)	24.86 (4.62)	24.76 (4.64)
BMI Categories				
< 30 kg/m^2	46 (90.2%)	48 (98.0%)	45 (90.0%)	139 (92.7%)
≥ 30 kg/m^2	5 (9.8%)	1 (2.0%)	5 (10.0%)	11 (7.3%)

BLV = bulevirtide (GS-4438), formerly known as Myrcludex B (MXB); BMI = body mass index; IQR = interquartile range; Q1 = first quartile; Q3 = third quartile
Percentages were based on the number of participants within each treatment group.
For the full analysis set, participants are analyzed as randomized (ie, planned treatment).
Body mass index (BMI) = computed as the body weight in kg divided by the squared height in meters.
Source: Section 15.1, Table 14.1.3-1

Disease characteristics at baseline

Table 2 MYR301: Baseline Disease Characteristics (Full Analysis Set)

Table 10. MYR301: Baseline Disease Characteristics (Full Analysis Set)

Characteristic	Delayed Treatment (N = 51)	BLV 2 mg (N = 49)	BLV 10 mg (N = 50)	Total (N = 150)
Cirrhosis Status (n, %)				
Present	24 (47.1%)	23 (46.9%)	24 (48.0%)	71 (47.3%)
Absent	27 (52.9%)	26 (53.1%)	26 (52.0%)	79 (52.7%)
Child-Pugh Score[a]				
Mean (SD)	5.2 (0.4)	5.3 (0.5)	5.3 (0.5)	5.3 (0.4)
Median (IQR)	5.0 (0.0)	5.0 (1.0)	5.0 (1.0)	5.0 (1.0)
Child-Pugh Class[a]				
A	24 (100.0%)	23 (100.0%)	24 (100.0%)	71 (100.0%)
HDV Genotype				
Genotype 1	51 (100.0%)	49 (100.0%)	48 (96.0%)	148 (98.7%)
Genotype 5	0	0	1 (2.0%)	1 (0.7%)
Missing	0	0	1 (2.0%)	1 (0.7%)
HBV Genotype[b]				
Genotype A	4 (7.8%)	2 (4.1%)	3 (6.0%)	9 (6.0%)
Genotype D	39 (76.5%)	44 (89.8%)	43 (86.0%)	126 (84.3%)
Genotype E	0	0	1 (2.0%)	1 (0.7%)
No data	8 (15.7%)	3 (6.1%)	3 (6.0%)	14 (9.3%)

Characteristic	Delayed Treatment (N = 51)	BLV 2 mg (N = 49)	BLV 10 mg (N = 50)	Total (N = 150)
HBV DNA (log_{10} IU/mL)				
n/nmiss	51/0	47/2	47/3	145/5
Mean (SD)	0.885 (0.989)	1.284 (1.300)	1.068 (1.273)	1.074 (1.193)
HDV RNA (log_{10} IU/mL)				
n/nmiss	51/0	48/1	50/0	149/1
Mean (SD)	5.077 (1.358)	5.096 (1.207)	4.961 (1.461)	5.044 (1.340)
HBeAg Status, n (%)				
Negative	47 (92.2%)	45 (91.8%)	43 (86.0%)	135 (90.0%)
HBsAg (log_{10} IU/mL)				
n/nmiss	51/0	47/2	47/3	145/5
Mean (SD)	3.676 (0.465)	3.671 (0.515)	3.614 (0.593)	3.654 (0.523)
ALT (U/L)				
Mean (SD)	101.6 (61.9)	107.9 (62.5)	123.4 (80.6)	110.9 (69.0)
Previous IFN Therapy				
No	22 (43.1%)	23 (46.9%)	21 (42.0%)	66 (44.0%)
Yes	29 (56.9%)	26 (53.1%)	29 (58.0%)	84 (56.0%)

ALT = alanine aminotransferase; BLV = bulevirtide (GS-4438), formerly known as Myrcludex B (MXB); HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HDV = hepatitis delta virus; IFN = interferon; IQR = interquartile range; n/nmiss = number of participants with evaluable/missing data; Q1 = first quartile; Q3 = third quartile

a Child-Pugh score and class are presented for cirrhotic participants only, with percentages based on the number of cirrhotic participants.

b These data are not from the central laboratory and are different than what was provided for the interim Week 24 analysis. These are derived from the updated analysis provided in the Virology Study Report (See Appendix 16.1.10).

Percentages are based on the number of participants within each treatment group.

For the Full Analysis Set, participants were analyzed as randomized (ie, planned treatment).

At baseline, 47.3% of participants overall had cirrhosis, and all these participants were Child-Pugh Class A; the mean (SD) Child-Pugh score was 5.3 (0.4) and all had a Child-Pugh A score below 7.

Concomitant Medications

The most common concomitant medications were in the following drug classes:

- Delayed treatment group: antivirals for systemic use (62.7%, 32 of 51 participants), vitamins and anesthetics (19.6%, 10 of 51 participants each), and analgesics (13.7%, 7 of 51 participants

- BLV 2 mg treatment group: antivirals for systemic use (63.3%, 31 of 49 participants), vitamins (24.5%, 12 of 49 participants), and analgesics and drugs for acid-related disorders (22.4%, 11 of 49 participants)

- BLV 10 mg treatment group: antivirals for systemic use (54.0%, 27 of 50 participants), vitamins (18.0%, 9 of 50 participants), and anesthetics (16.0%, 8 of 50 participants)

Antivirals for systemic use were the most common drug class.
In the study, 30% (45 of 150) of participants had prior use of any anti-HBV medication while 60% (90 of 150) of participants had concomitant use of any anti-HBV medication during the first 48 weeks of the study. The most common anti-HBV medications used during the study were tenofovir (not specified) (delayed treatment group 27.5%, 14 participants; BLV 2 mg treatment group: 32.7%, 16 participants; BLV 10 mg treatment group: 24.0%, 12 participants), TDF (delayed treatment group 29.4%, 15 participants; BLV 2 mg Bulevirtide treatment group: 16.3%, 8 participants; BLV 10 mg treatment group: 18.0%, 9 participants), and entecavir (delayed treatment group 13.7%, 7 participants; BLV 2 mg treatment group: 14.3%, 7 participants; BLV 10 mg treatment group: 10.0%, 5 participants).

Primary Efficacy End Point

The primary efficacy end point was the combined response at Week 48 of treatment, which was defined as fulfilment of 2 conditions simultaneously: undetectable HDV RNA (HDV RNA < LOD) or decrease in HDV RNA by ≥ 2 $\log_{10}$ IU/mL from baseline, and ALT normalization. An interim analysis of the combined response was performed also at week 24.
The proportion of participants achieving the combined response increased from Week 24 to Week 48 in the BLV treatment groups. The combined response rates (95% CI) at Week 48 were 44.9% (30.7% to 59.8%) and 48.0% (33.7% to 62.6%) in treatment groups BLV 2 mg and BLV 10 mg, versus 2.0% (0.0% to 10.4%) in the delayed treatment group (Table 3).
The differences in proportions of responders at Week 48 for the combined response between each of the BLV treatment groups and the delayed treatment group were statistically significant (***Table 3***).

Table 3. MYR301: Achievement of Combined Response at Week 24 and Week 48—Statistical Analysis of Difference in Proportions of Participants for Each Treatment Group Using Fisher's Exact Test (Full Analysis Set)

Combined Response	Delayed Treatment (N = 51)	BLV 2 mg (N = 49)	BLV 10 mg (N = 50)
Week 24[a]			
Number of Participants in Analysis	51	49	50
Number of Responders	0	18	14
Proportion Responders (95% CI)	0 (0.0%, 7.0%)	36.7% (23.4%, 51.7%)	28.0% (16.2%, 42.5%)
Difference in Proportions (99% CI)	—	36.7 (20.0, 56.1)	28.0 (12.9, 47.1)
P Value[b]	—	< 0.0001	< 0.0001
Week 48			
Number of Participants in Analysis	51	49	50
Number of Responders	1	22	24
Proportion Responders (95% CI)	2.0% (0.0%, 10.4%)	44.9% (30.7%, 59.8%)	48.0% (33.7%, 62.6%)
Difference in Proportions (96% CI)	—	42.9 (27.0, 58.5)	46.0 (30.5, 61.4)
P Value[c]	—	< 0.0001	< 0.0001

BLV = bulevirtide (GS-4438), formerly known as Myrcludex B; HDV = hepatitis delta virus; RNA = ribonucleic acid

Interim result.

There was a statistically significant difference at Week 24 if $P < 0.01$.

There was a statistically significant difference at Week 48 if $P < 0.04$.

The comparison of BLV 2 mg versus delayed treatment was considered significant only if the comparison of 10 mg versus delayed treatment was significant as well.

Combined response was defined as (undetectable HDV RNA or decrease in HDV RNA by ≥ 2 log10 IU/mL from baseline) and alanine aminotransferase normalization.

The CI was calculated using Clopper-Pearson (exact) for within-group proportions and exact unconditional for difference in proportions.

A confidence level of 95% was used for within-group CIs. For difference in proportions, the confidence level used was 99% for 24 weeks (Week 24 interim analysis) and 96% for Week 48 (Week 48 primary end point analysis).

Fisher's exact tests were used for each comparison of BLV 2 mg and 10 mg versus delayed treatment using a significance level of 0.01 at Week 24 and 0.04 at Week 48.

Secondary Efficacy End Points

Undetectable HDV RNA at Week 48 (Key Secondary End Point)

The proportion of responders (95% CI) with undetectable HDV RNA was 12.2% (4.6% to 24.8%) and 20.0% (10.0% to 33.7%) in BLV 2 mg and BLV 10 mg treatment groups, respectively (Table 4). The difference in proportions of responders (96% CI) at Week 48 with undetectable HDV RNA between the 2 mg and 10 mg BLV groups was not statistically significant ($P = 0.4139$).

Table 4. MYR301: Undetectable HDV RNA at Week 24 and Week 48—Statistical Analysis of the Difference in Proportions of Participants in the Bulevirtide Treatment Groups (Bulevirtide 2 mg and 10 mg) Using Fisher's Exact Test (Full Analysis Set)

	BLV 2 mg (N = 49)	**BLV 10 mg (N = 50)**
Week 24[a]		
Number of Participants Included in Analysis	49	50
Number of Responders	3	4
Proportion Responders (95% CI)	6.1% (1.3%, 16.9%)	8.0% (2.2%, 19.2%)
Difference in Proportions (99% CI)	—	1.9 (−14.8, 18.8)
P Value[b]	—	1.0000
Week 48		
Number of Participants Included in Analysis	49	50
Number of Responders	6	10
Proportion Responders (95% CI)	12.2% (4.6%, 24.8%)	20.0% (10.0%, 33.7%)
Difference in Proportions (96% CI)	—	7.8 (−8.5, 24.3)
P Value[c]	—	0.4139

BLV = bulevirtide (GS-4438), formerly known as Myrcludex; HDV = hepatitis delta virus
a Interim result.
b There was a statistically significant difference at Week 24 if $P < 0.01$.
c There was a statistically significant difference at Week 48 if $P < 0.04$.
The CI was calculated using Clopper-Pearson (exact) for within-group proportions and exact unconditional for difference in proportions.
A confidence level of 95% was used for within-group CIs. For difference in proportions, the confidence level used was 99% for 24 weeks (Week 24 interim analysis) and 96% for Week 48 (Week 48 secondary end point analysis).
Fisher's exact tests were used for comparison of BLV 10 mg versus BLV 2 mg and using a significance level of 0.01 at Week 24 and 0.04 at Week 48.
For missing values, the last-observation-carried-forward approach was used if COVID-19 related, and the missing-equals-failure approach otherwise.
For the Full Analysis Set, participants were analyzed as randomized (ie, planned treatment).

Alanine Aminotransferase Normalization at Week 48

At Week 48, 51.0% and 56.0%, respectively in the in the 2 mg and 10 mg BLV treatment arms achieved ALT normalisation. In the delayed treatment group, the proportion of participants with ALT normalization at Week 48 was 11.8%. These analyses were not type I error controlled.

Table 5 MYR301: ALT Normalization at Week 24 and Week 48 – Statistical Analysis of Difference in Proportions of Participants for Each Treatment Group, Using Fisher`s Exact Test (Full Analysis Set)

ALT Normalization	Delayed Treatment (N = 51)	BLV 2 mg (N = 49)	BLV 10 mg (N = 50)
Week 24			
Number of Participants Included in Analysis	51	49	50
Number With ALT Normalization	3	26	19
Proportion (95% CI)	5.9% (1.2% to 16.2%)	53.1% (38.3%, 67.5%)	38.0% (24.7%, 52.8%)
Difference in Proportions (95% CI)	—	47.2 (30.6, 62.5)	32.1 (15.9, 47.5)
P Value	—	< 0.0001	< 0.0001
Week 48			
Number of Participants Included in Analysis	51	49	50
Number With ALT Normalization	6	25	28
Proportion (95% CI)	11.8% (4.4%, 23.9%)	51.0% (36.3%, 65.6%)	56.0% (41.3%, 70.0%)
Difference in Proportions (95% CI)	—	39.3 (19.9, 55.8)	44.2 (25.8, 59.9)
P Value	—	< 0.0001	< 0.0001

ALT = alanine aminotransferase; BLV = bulevirtide (GS-4438), formerly known as Myrcludex B (MXB); HDV = hepatitis delta virus; M = F = missing equals failure
The CI was calculated using Clopper-Pearson (exact) for within-group proportions and exact unconditional for difference in proportions.
A confidence level of 95% was used for within-group CIs and for CIs for difference in proportions.
Fisher's exact tests were used for each comparison of BLV 2 mg and 10 mg versus delayed treatment using a significance level of 0.05.
For missing values, the M = F approach was used.

Change from Baseline in Liver Stiffness at Week 48

In Study MYR301, liver stiffness was measured at baseline and at Week 48 by FibroScan. The mean (SD) liver stiffness at baseline was 13.99 (8.19) kPa in the BLV 2 mg treatment group, 14.81 (9.26) kPa in the BLV 10 mg treatment group, and 15.26 (8.95) kPa in the delayed treatment group. There was a mean decrease in liver stiffness in both of the BLV treatment groups.

At Week 48, the LS means (95% CI) for change from baseline in liver stiffness was−3.08 kPa for the BLV 2 mg treatment group, −3.17 kPa for BLV 10 mg treatment group, and 0.88 kPa for the delayed treatment group. These analyses were not type I error controlled (***Table 6***).

Table 6. MYR301: Change From Baseline in Liver Stiffness (FibroScan, kPA) at Week 48 – Statistical Analysis of Difference Versus Control Using ANCOVA (Full Analysis Set)

Liver Stiffness (kPa)	Delayed Treatment (N = 51)	BLV 2 mg (N = 49)	BLV 10 mg (N = 50)
Baseline			
Mean (SD)	15.26 (8.95)	13.99 (8.19)	14.81 (9.26)
Week 48			
Number of Participants in Analysis	45	48	42
LS Means (95% CI)	0.88 (−0.80, 2.56)	−3.08 (−4.70, −1.46)	−3.17 (−4.90, −1.44)
Difference in LS Means (95% CI)	—	−3.96 (−6.28, −1.64)	−4.05 (−6.45, −1.66)
P Value	—	0.0010	0.0010

ANCOVA = analysis of covariance, BLV = bulevirtide (GS-4438), formerly known as Myrcludex B (MXB); LS = least squares
An ANCOVA model was used to test null hypotheses of no difference compared with the control group.
Change from baseline at Week 48 in liver stiffness was the dependent variable.
The model included treatment, region, presence of cirrhosis as fixed-effect factors, and baseline liver stiffness as covariate.
For the Full Analysis Set, participants were analyzed as randomized (ie, planned treatment).
Source: Section 15.1, Table 14.2.2.3-1, Table 14.1.3-23

Similar results were observed when the analyses were performed for the PP Analysis Set (Section 15.1, Table 14.2.2.3-2).

Additional Efficacy End Point

Viral response was defined as HDV RNA decrease by ≥ 2 $\log_{10}$ IU/mL from baseline or undetectable HDV RNA at Week 48. The proportions of participants who achieved a viral response at Week 48 were 71.4% (95% CI: 56.7% to 83.4%) in the BLV 2 mg treatment group, 76.0% (95% CI: 61.8% to 85.9%) in the BLV 10 mg treatment group, and 3.9% (95% CI: 0.5% to 13.5%) in the delayed treatment group These analyses were not type I error controlled.

Exploratory Efficacy End Points

Fibrosis and Histological Activity

Assessments of liver fibrosis and changes in histological activity were performed only for those participants who underwent liver biopsy at baseline and Week 48: 25 of 49 participants (51.0%) in the BLV 2 mg group, 31 of 50 participants (62.0%) in the BLV 10 mg group, and 26 of 51 participants (51.0%) in the delayed treatment group. Table 5 presents the change from baseline in fibrosis at Week 48 in the full analysis set. Improvements in fibrosis and necroinflammation (histological activity stage) parameters were generally seen in the BLV treatment groups compared with the delayed treatment group. The percentages of participants who had an improvement (i.e., decrease of at least 1 point) in the fibrosis parameters (Ishak fibrosis score, Knodell fibrosis score, and Metavir fibrosis stage) at Week 48 were numerically higher in each of the BLV treatment groups than in the delayed treatment group, particularly for the Metavir and Knodell scoring systems. The percentages of participants who had an improvement in the fibrosis parameters were similar for the BLV 2 mg and BLV 10 mg treatment groups.

Table 7.MYR301: Change in Fibrosis From Baseline to Week 48 (Full Analysis Set)

Change in Fibrosis (n/N [%])	Delayed Treatment (N = 51)	BLV 2 mg (N = 49)	BLV 10 mg (N = 50)
Ishak Fibrosis Score			
Improvement	13/26 (50.0%)	14/25 (56.0%)	17/31 (54.8%)
95% CI	(29.9%, 70.1%)	(34.9%, 75.6%)	(36.0%, 72.7%)
No Change	6/26 (23.1%)	6/25 (24.0%)	10/31 (32.3%)
95% CI	(9.0%, 43.6%)	(9.4%, 45.1%)	(16.7%, 51.4%)
Worsening	7/26 (26.9%)	5/25 (20.0%)	4/31 (12.9%)
95% CI	(11.6%, 47.8%)	(6.8%, 40.7%)	(3.6%, 29.8%)
Missing	25/51 (49.0%)	24/49 (49.0%)	19/50 (38.0%)

Change in Fibrosis (n/N [%])	Delayed Treatment (N = 51)	BLV 2 mg (N = 49)	BLV 10 mg (N = 50)
Knodell Fibrosis Score			
Improvement	9/26 (34.6%)	14/25 (56.0%)	14/31 (45.2%)
95% CI	(17.2%, 55.7%)	(34.9%, 75.6%)	(27.3%, 64.0%)
No Change	9/26 (34.6%)	6/25 (24.0%)	11/31 (35.5%)
95% CI	(17.2%, 55.7%)	(9.4%, 45.1%)	(19.2%, 54.6%)
Worsening	8/26 (30.8%)	5/25 (20.0%)	6/31 (19.4%)
95% CI	(14.3%, 51.8%)	(6.8%, 40.7%)	(7.5%, 37.5%)
Missing	25/51 (49.0%)	24/49 (49.0%)	19/50 (38.0%)
Metavir Fibrosis Stage			
Improvement	10/26 (38.5%)	13/25 (52.0%)	15/31 (48.4%)
95% CI	(20.2%, 59.4%)	(31.3%, 72.2%)	(30.2%, 66.9%)
No Change	8/26 (30.8%)	6/25 (24.0%)	10/31 (32.3%)
95% CI	(14.3%, 51.8%)	(9.4%, 45.1%)	(16.7%, 51.4%)
Worsening	8/26 (30.8%)	6/25 (24.0%)	6/31 (19.4%)
95% CI	(14.3%, 51.8%)	(9.4%, 45.1%)	(7.5%, 37.5%)
Missing	25/51 (49.0%)	24/49 (49.0%)	19/50 (38.0%)

BLV = bulevirtide (GS-4438), formerly known as Myrcludex B (MXB)
Percentages were based on the number of participants within each treatment group with observed data.
Percentage for the missing category was based on number of participants within each treatment group.
Improvement was defined as a decrease of at least 1 point; worsening was defined as an increase of at least 1 point.
Assessment of improvement/worsening was based on categorized scores.

Table 8 presents the change from baseline in histological activity stage at Week 48. The histological activity stage parameters (histological activity index and Metavir activity grade), the percentages of participants who had an improvement (i.e., decrease of at least 1 point) at Week 48 were numerically higher in each of the BLV treatment groups than in the delayed treatment group. The percentage of participants who had an improvement in the histological activity stage parameters was similar for the BLV 2 mg and BLV 10 mg treatment groups.

Table 8. MYR301: Change in Histological Activity Stage From Baseline to Week 48 (Full Analysis Set)

Change in Histological Activity Stage (n/N [%])	Delayed Treatment (N = 51)	BLV 2 mg (N = 49)	BLV 10 mg (N = 50)
Metavir Activity Grade			
Improvement	11/26 (42.3%)	17/25 (68.0%)	22/31 (71.0%)
95% CI	(23.4%, 63.1%)	(46.5%, 85.1%)	(52.0%, 85.8%)
No Change	13/26 (50.0%)	7/25 (28.0%)	9/31 (29.0%)
95% CI	(29.9%, 70.1%)	(12.1%, 49.4%)	(14.2%, 48.0%)
Worsening	2/26 (7.7%)	1/25 (4.0%)	0
95% CI	(0.9%, 25.1%)	(0.1%, 20.4%)	(0.0%, 11.2%)
Missing	25/51 (49.0%)	24/49 (49.0%)	19/50 (38.0%)
Histological Activity Index			
Improvement	4/26 (15.4%)	15/25 (60.0%)	21/31 (67.7%)
95% CI	(4.4%, 34.9%)	(38.7%, 78.9%)	(48.6%, 83.3%)
No Change	13/26 (50.0%)	9/25 (36.0%)	8/31 (25.8%)
95% CI	(29.9%, 70.1%)	(18.0%, 57.5%)	(11.9%, 44.6%)
Worsening	9/26 (34.6%)	1/25 (4.0%)	2/31 (6.5%)
95% CI	(17.2%, 55.7%)	(0.1%, 20.4%)	(0.8%, 21.4%)
Missing	25/51 (49.0%)	24/49 (49.0%)	19/50 (38.0%)

BLV = bulevirtide (GS-4438), formerly known as Myrcludex B (MXB)
Percentages were based on the number of participants within each treatment group with observed data.
Percentage for the missing category was based on number of participants within each treatment group.
Improvement was defined as a decrease of at least 1 point; worsening was defined as an increase of at least 1 point.
Assessment of improvement/worsening was based on categorized scores.

Serological Analyses

HBsAg loss with or without seroconversion at Week 48:

No participant across the treatment groups experienced HBsAg loss and no participant across treatment groups experienced HBsAg seroconversion by Week 48.

HBsAg response at Week 48:
HBsAg response was defined as HBsAg decrease by > 1 $\log_{10}$ IU/mL at postbaseline assessment. The difference in proportions of participants at Week 48 for the HBsAg response between each of the BLV treatment groups and the delayed treatment group was not statistically significant.

Table 9. HBsAG Response at Week 24 and 48. Statistical analysis of difference in proportions, using Fisher`s exact test. Full analysis set

HBsAg response	Delayed treatment (N=51)	Bulevirtide 2mg (N=49)	Bulevirtide 10mg (N=50)
Week 24			
Number of subjects in analysis	51	49	50
Number of responders	0	1	0
Proportion Responders (95% CI)	0 (0.0%, 7.0%)	2.0% (0.1%, 10.9%)	0 (0.0%, 7.1%)
Difference in proportions (95% CI)		2.0 (-5.2, 10.9)	-
p-value		0.4900	-
Week 48			
Number of subjects in analysis	51	49	50
Number of responders	1	0	0
Proportion Responders (95% CI)	2.0% (0.0%, 10.4%)	0 (0.0%, 7.3%)	0 (0.0%, 7.1%)
Difference in proportions (95% CI)		-2.0 (-10.6, 5.6)	-2.0 (-10.6, 5.6)
p-value		1.0000	1.0000

HBsAg response is defined HBsAg decrease by >1 log10 IU/mL.
Proportions in percent are based on the number of subjects in analysis within each treatment group.
CI = Confidence interval, calculated using Clopper-Pearson (exact) for within group proportions and exact unconditional for difference in proportions.
Fisher's exact tests were used for each comparison of Bulevirtide 2mg and 10mg versus Delayed treatment using a significance level of 0.05.
For missing values, the missing equals failure (MEF) approach was used.
For the full analysis set, subjects are analysed as randomised (i.e. planned treatment).
Program: \Subprogs\Tables\EFFx HBsAg response.sas
Date and time program was run: 2022-06-29T08:19. Date and time analysis database was run: 2022-06-14T19:03

Change from baseline in HBsAg levels ($\log_{10}$ scale):
Change from baseline for HBsAg levels ($\log_{10}$ scale) at Week 48, as measured by LS means, was minimal and similar across treatment groups.

Table 10. Change from baseline HBsAg levels (log-10 scale). Statistical analysis of difference vs control, using MMRM analysis. Full analysis set.

HBsAg [log-10 IU/mL]	Delayed treatment (N=51)	Bulevirtide 2mg (N=49)	Bulevirtide 10mg (N=50)
Number of subjects in analysis[a]	51	47	46
Week 24			
LS means (95% CI)	-0.062 (-0.115, -0.008)	-0.032 (-0.087, 0.024)	0.039 (-0.017, 0.095)
Difference in LS means (95% CI)		0.030 (-0.047, 0.107)	0.101 (0.023, 0.178)
p-value		0.4381	0.0111
Week 48			
LS means (95% CI)	0.006 (-0.085, 0.097)	0.053 (-0.041, 0.147)	0.115 (0.019, 0.211)
Difference in LS means (95% CI)		0.047 (-0.084, 0.178)	0.109 (-0.023, 0.241)
p-value		0.4799	0.1054

LS = least squares, CI = confidence interval.
A mixed-effects model for repeated measures (MMRM) was used to test null hypotheses of no difference compared to the control group. Change from baseline in HBsAg (log10-transformed) was the dependent variable using data for all post-baseline analysis visits up to Week 48.
The model included treatment, region, presence of cirrhosis, visit and treatment-by-visit interaction as fixed-effect factors, and baseline HBsAg (log10-transformed) as covariate.
[a] Number of subjects with at least one post baseline value used for the estimates, where 1 subject in the 2mg group has been excluded due to missing baseline value. All subjects in FAS are included in the MMRM model.
For the full analysis set, subjects are analysed as randomised (i.e. planned treatment).
Program: \Subprogs\Tables\EFFx HBsAg levels.sas
Date and time program was run: 2022-06-29T08:19. Date and time analysis database was run: 2022-06-14T19:03

HBeAg loss with or without seroconversion at Week 48:

For the small subset of participants who were HBeAg positive at baseline, which included 4 participants (7.8%) in the delayed treatment group, 4 participants (8.2%) in the BLV 2 mg treatment group, and 7 participants (14.0%) in the BLV 10 mg treatment group, there were no participants across the 3 treatment groups who experienced HBeAg loss by Week 48.

HBV DNA levels

A total of 45 participants (30%) had used nucleoside/nucleotide analogues prior to the start of the study, and during the first 48 weeks of treatment, 90 participants (60%) were treated with nucleoside/nucleotide analogues. All anti-HBV treatment was initiated prior to or at baseline (by Day 2), with similar proportions receiving anti-HBV across the 3 treatment groups. At baseline, mean HBV DNA levels were low (< 1.5 $\log_{10}$ IU/mL) overall and comparable between treatment groups (***Table 11***). At Week 48, the LS means change in HBV DNA levels was small in all treatment groups.

Table 11. MYR301: Change from baseline in HBV DNA levels ($\log_{10}$ Scale) at Week 48 - Statistical analysis of difference versus Control Using MMRM Analysis (Full analysis set)

HBV DNA [$\log_{10}$ IU/mL]	Delayed Treatment (N = 51)	BLV 2 mg (N = 49)	BLV 10 mg (N = 50)
Number of Participants In Analysis	51	47	46
LS Means (95% CI)	−0.163 (−0.404, 0.078)	−0.384 (−0.634, −0.134)	−0.643 (−0.898, −0.387)
Difference in LS Means (95% CI)	—	−0.221 (−0.568, 0.126)	−0.480 (−0.830, −0.129)
P-Value	—	0.2100	0.0077

BLV = bulevirtide (GS-4438), formerly known as Myrcludex B (MXB); HBV = hepatitis B virus; LS = least squares; MMRM = mixed-effects model for repeated measures
An MMRM was used to test null hypotheses of no difference compared with the control group.
Change from baseline in HBV DNA ($\log_{10}$-transformed) was the dependent variable using data for all postbaseline analysis visits up to Week 48.
The model included treatment, region, presence of cirrhosis, visit and treatment-by-visit interaction as fixed-effect factors, and baseline HBV DNA ($\log_{10}$ transformed) as covariate.

Quality-of-Life-Questionnaires

Quality of life assessments were conducted in Study MYR301. At Week 48, scores for the individual EuroQol (5 dimensions) domains, EuroQol visual analogue scale, Fatigue Severity Scale, and the Hepatitis Quality of Life Questionnaire (HQLQ) components were generally similar between each of the BLV treatment groups when compared with the delayed treatment group, with the exception of role physical of the HQLQ, in which there was an improvement between the BLV treatment groups and the delayed treatment group.

Comparison of Results in Subpopulations for Week 48

Comparison of Results in Cirrhosis Subpopulations

Efficacy subgroups for the primary, secondary, and exploratory efficacy end points in Study MYR301 were based on the presence of cirrhosis.

Subgroup Analysis of Combined Response (Primary Efficacy End Point)

The combined response rate in the BLV 2 mg group was lower in participants with cirrhosis (34.8%) (95% CI: 16.4% to 57.3%) than in participants without cirrhosis (53.8%) (95% CI: 33.4% to 73.4%), a likely

reflection of the lower ALT normalization rates seen in participants with cirrhosis. In the BLV 10 mg group, the combined response rate was similar for participants with and without cirrhosis**:** 50.0% (95% CI: 29.1% to 70.9%) of participants with cirrhosis versus 46.2% (95% CI: 26.6% to 66.6%) of participants without cirrhosis achieved a combined response.

Table 12. Combined Response at Week 24 and 48. Frequency table. Full analysis set, subgroup of subjects with cirrhosis.

Combined response	Delayed treatment (N=24)	Bulevirtide 2mg (N=23)	Bulevirtide 10mg (N=24)	Total (N=71)
Week 24				
Responder	0	6 (26.1%)	6 (25.0%)	12 (16.9%)
Non-responder	24 (100.0%)	17 (73.9%)	18 (75.0%)	59 (83.1%)
Week 48				
Responder	1 (4.2%)	8 (34.8%)	12 (50.0%)	21 (29.6%)
Non-responder	23 (95.8%)	15 (65.2%)	12 (50.0%)	50 (70.4%)

Combined response is defined as (Undetectable HDV RNA or decrease in HDV RNA by ≥2 log10 IU/mL from bl) and ALT nor malisation.
Percentages are based on the number of subjects within each treatment group
For missing values, the last observation carrying forward (LOCF) approach was used if COVID-19 related, and the missing equals failure (MEF) approach otherwise.
For the full analysis set, subjects are analysed as randomised (i.e. planned treatment).
Program: \Subprogs\Tables\EFF1 Combined Response.sas
Date and time program was run: 2022-06-29T08:15. Date and time analysis database was run: 2022-06-14T19:03

Table 13. Combined Response at Week 24 and 48. Frequency table. Full analysis set, subgroup subjects without cirrhosis.

Combined response	Delayed treatment (N=27)	Bulevirtide 2mg (N=26)	Bulevirtide 10mg (N=26)	Total (N=79)
Week 24				
Responder	0	12 (46.2%)	8 (30.8%)	20 (25.3%)
Non-responder	27 (100.0%)	14 (53.8%)	18 (69.2%)	59 (74.7%)
Week 48				
Responder	0	14 (53.8%)	12 (46.2%)	26 (32.9%)
Non-responder	27 (100.0%)	12 (46.2%)	14 (53.8%)	53 (67.1%)

Combined response is defined as (Undetectable HDV RNA or decrease in HDV RNA by ≥2 log10 IU/mL from bl) and ALT nor malisation.
Percentages are based on the number of subjects within each treatment group
For missing values, the last observation carrying forward (LOCF) approach was used if COVID-19 related, and the missing equals failure (MEF) approach otherwise.
For the full analysis set, subjects are analysed as randomised (i.e. planned treatment).
Program: \Subprogs\Tables\EFF1 Combined Response.sas
Date and time program was run: 2022-06-29T08:16. Date and time analysis database was run: 2022-06-14T19:03

Subgroup Analysis of Undetectable HDV RNA Response (Secondary Efficacy End Point)

Percentages of participants with undetectable HDV RNA for BLV 2 mg was higher for the participants with cirrhosis (21.7%) compared to participants without cirrhosis (3.8%). For BLV 10 mg group, percentages of participants with undetectable HDV RNA were similar for the participants with cirrhosis (25.0%) than in participants without cirrhosis (15.4%).

Table 14. Frequency table for Undetectable HDV RNA at Week 24 and 48. Full analysis set, subgroup of subjects with cirrhosis.

Undetectable HDV RNA	Delayed treatment (N=24)	Bulevirtide 2mg (N=23)	Bulevirtide 10mg (N=24)	Total (N=71)
Week 24				
Responder	0	2 (8.7%)	3 (12.5%)	5 (7.0%)
Non-responder	24 (100.0%)	21 (91.3%)	21 (87.5%)	66 (93.0%)
Week 48				
Responder	0	5 (21.7%)	6 (25.0%)	11 (15.5%)
Non-responder	24 (100.0%)	18 (78.3%)	18 (75.0%)	60 (84.5%)

Percentages are based on the number of subjects within each treatment group
For missing values, the last observation carrying forward (LOCF) approach was used if COVID-19 related, and the missing equals failure (MEF) approach otherwise.
For the full analysis set, subjects are analysed as randomised (i.e. planned treatment).
Program: \Subprogs\Tables\EFF2 Undetectable HDV RNA.sas
Date and time program was run: 2022-06-29T08:16. Date and time analysis database was run: 2022-06-14T19:03

Table 15. Frequency table for Undetectable HDV RNA at Week 24 and 48. Full analysis set, subgroup of subjects with cirrhosis

Undetectable HDV RNA	Delayed treatment (N=27)	Bulevirtide 2mg (N=26)	Bulevirtide 10mg (N=26)	Total (N=79)
Week 24				
Responder	0	1 (3.8%)	1 (3.8%)	2 (2.5%)
Non-responder	27 (100.0%)	25 (96.2%)	25 (96.2%)	77 (97.5%)
Week 48				
Responder	0	1 (3.8%)	4 (15.4%)	5 (6.3%)
Non-responder	27 (100.0%)	25 (96.2%)	22 (84.6%)	74 (93.7%)

Percentages are based on the number of subjects within each treatment group
For missing values, the last observation carrying forward (LOCF) approach was used if COVID-19 related, and the missing equals failure (MEF) approach otherwise.
For the full analysis set, subjects are analysed as randomised (i.e. planned treatment).
Program: \Subprogs\Tables\EFF2 Undetectable HDV RNA.sas
Date and time program was run: 2022-06-29T08:16. Date and time analysis database was run: 2022-06-14T19:03

Subgroup Analysis of Biochemical Response (Secondary Efficacy End Point)

In the BLV 2 mg group, the percentage of participants with cirrhosis who had normalized ALT (39.1%) was lower than the percentage of participants without cirrhosis who had normalized ALT (61.5%). In the BLV 10 mg group, the percentage of participants with cirrhosis who had normalized ALT (50.0%) was similar to the percentage of participants without cirrhosis who had normalized ALT (61.5%).

Table 16. Frequency table for Undetectable HDV RNA at Week 24 and 48. Full analysis set, subgroup of subjects with cirrhosis

ALT normalisation	Delayed treatment (N=24)	Bulevirtide 2mg (N=23)	Bulevirtide 10mg (N=24)	Total (N=71)
Week 24				
Normal	2 (8.3%)	10 (43.5%)	6 (25.0%)	18 (25.4%)
Abnormal	22 (91.7%)	13 (56.5%)	18 (75.0%)	53 (74.6%)
Week 48				
Normal	4 (16.7%)	9 (39.1%)	12 (50.0%)	25 (35.2%)
Abnormal	20 (83.3%)	14 (60.9%)	12 (50.0%)	46 (64.8%)

Percentages are based on the number of subjects within each treatment group
For missing values, the missing equals failure (MEF) approach was used.
For the full analysis set, subjects are analysed as randomised (i.e. planned treatment).
Program: \Subprogs\Tables\EFF2 ALT normalisation.sas
Date and time program was run: 2022-06-29T08:17. Date and time analysis database was run: 2022-06-14T19:03

Table 14.2.2.2-7. Frequency table for ALT at Week 24 and 48. Full analysis set, subgroup of subjects without cirrhosis.

ALT normalisation	Delayed treatment (N=27)	Bulevirtide 2mg (N=26)	Bulevirtide 10mg (N=26)	Total (N=79)
Week 24				
Normal	1 (3.7%)	16 (61.5%)	13 (50.0%)	30 (38.0%)
Abnormal	26 (96.3%)	10 (38.5%)	13 (50.0%)	49 (62.0%)
Week 48				
Normal	2 (7.4%)	16 (61.5%)	16 (61.5%)	34 (43.0%)
Abnormal	25 (92.6%)	10 (38.5%)	10 (38.5%)	45 (57.0%)

Percentages are based on the number of subjects within each treatment group
For missing values, the missing equals failure (MEF) approach was used.
For the full analysis set, subjects are analysed as randomised (i.e. planned treatment).
Program: \Subprogs\Tables\EFF2 ALT normalisation.sas
Date and time program was run: 2022-06-29T08:17. Date and time analysis database was run: 2022-06-14T19:03

Additional Subgroup Analysis

Analysis of these additional subgroups was conducted solely for the primary end point of combined response at Week 48.

Age Group (< 45, ≥ 45 years): In the BLV 2 mg group, the combined response rate was lower in participants < 45 years of age (35.7%) (95% CI: 18.6% to 55.9%) than in participants ≥ 45 years of age (57.1%) (95% CI: 34.0% to 78.2%). In the BLV 10 mg group, the combined response rate was similar across age groups: 48.6% (95% CI: 31.4% to 66.0%) in participants < 45 years of age and 46.7% (95% CI: 21.3% to 73.4%) in participants ≥ 45 years of age achieved a combined response.

Sex at Birth: In the BLV 2 mg group, the combined response rate was similar across subgroups for sex at birth, with 43.3% (95% CI: 25.5% to 62.6%) of male participants and 47.4% (95% CI: 24.4% to 71.1%) of female participants achieving a combined response. In the BLV 10 mg group, the combined response rate was slightly higher for male participants (56.7%) (95% CI: 37.4% to 74.5%) than for female participants (35.0%) (95% CI: 15.4% to 59.2%).

Race (White, Other): In the BLV 2 mg group, the combined response rate was higher in White participants (48.8%) (95% CI: 32.9% to 64.9%) than Other participants (25.0%) (95% CI: 3.2% to 65.1%). In the BLV 10 mg group, the combined response rate was similar by race, with 46.5% (95% CI: 31.2% to 62.3%) of White participants and 57.1% (95% CI: 18.4% to 90.1%) of Other participants achieving a combined response. As the majority of participants in Study MYR301 were White (83.7% in the BLV 2 mg group; 86.0% in the BLV 10 mg group), the analysis and 95% CI likely reflects the small number of participants in the "other" category.

Baseline ALT (≤ 1.5 × ULN, > 1.5 × ULN): In the BLV 2 mg group, the combined response rate was similar across subgroups for baseline ALT levels, with 40.0% (95% CI: 12.2% to 73.8%) of participants with baseline ALT ≤ 1.5 × ULN and 46.2% (95% CI: 30.1% to 62.8%) of participants with baseline ALT > 1.5 × ULN achieving a combined response. In the BLV 10 mg group, the combined response rate was also similar, with 54.5% (95% CI: 23.4% to 83.3%) of participants with baseline ALT ≤ 1.5 × ULN and 46.2% (95% CI: 30.1% to 62.8%) of participants with baseline ALT > 1.5 × ULN achieving a combined response.

Baseline HDV RNA log_{10} (< Median, ≥ Median): In the BLV 2 mg group, the combined response rate was numerically higher in participants with HDV RNA log_{10} levels ≥ median baseline value (58.3%) (95% CI: 36.6% to 77.9%) compared with participants with baseline HDV RNA log_{10} levels < the median (33.3%) (95% CI: 15.6% to 55.3%). In the BLV 10 mg group, the combined response rate was numerically lower in participants with HDV RNA log_{10} levels ≥ baseline value (40.0%) (95% CI: 21.1% to 61.3%) compared with participants with baseline HDV RNA log_{10} levels < median (56.0%) (95% CI: 34.9% to 75.6%).

The MAH concludes that at Week 48, the combined response rates for BLV 2 mg were consistent across all major subgroups, including subgroups relating to cirrhosis status.

Immunogenicity Evaluation Results

Study MYR301

Two participants, both of whom were in the BLV 10 mg treatment group, were ADA-positive at baseline. By Week 16, 5 participants (10.2%) in the BLV 2 mg group and 5 participants (10.0%) in the BLV 10 mg group were ADA-positive. Over the 48-week treatment period, 22.4% (11 of 49) of participants treated in the BLV 2 mg group and 18.0% (9 of 50) of participants treated in the BLV 10 mg group were ADA-positive, indicating that ADA prevalence was not impacted by dose.

The change from baseline to Week 48 in the anti-BLV antibodies concentration showed a mean (SD) increase, with a larger increase seen in the BLV 10 mg group (345 [1294] ng/mL) in comparison to the BLV 2 mg group (127 [378] ng/mL).

The difference between Week 24 and Week 48 for ADA prevalence was small: the number of participants who were positive for ADA at Week 24 were 5 participants for the BLV 2 mg group and 7 participants for the BLV 10 mg group, and at Week 48 were 6 participants and 3 participants for the BLV 2 mg and BLV 10 mg groups, respectively; therefore, efficacy by ADA assessment was not repeated with the Week 48 data.

Table 17. ADA positivity overview for 2mg and 10 mg treatment groups

	Bulevirtide 2mg (N=49)	Bulevirtide 10mg (N=50)	Total (N=99)
ADA			
Positive	11 (22.4%)	9 (18.0%)	20 (20.2%)
Negative	38 (77.6%)	40 (80.0%)	78 (78.8%)
Missing	0	1 (2.0%)	1 (1.0%)

Integrated summary of immunogenicity and impact on efficacy in Studies MYR202, MYR203 and MYR301

MYR202 was a Phase 2, multicenter, open-label, randomized clinical study to assess efficacy and safety of 3 doses of bulevirtide for 24 weeks in combination with tenofovir compared to tenofovir alone to suppress HBV replication in patients with chronic hepatitis D. MYR203 was a Phase 2, multicenter, open-label, randomized, comparative, parallel arm phase 2 study to assess efficacy and safety of bulevirtide in combination with peginterferon alfa-2a versus peginterferon alfa-2a alone in patients with chronic viral hepatitis B with Delta-agent.

The incidence and prevalence up to Week 24 and Week 48 are summarized by treatment group (2mg and 10mg BLV monotherapy), see tables below.

There were no meaningful differences in efficacy endpoints (combined response, viral response, and ALT normalization) between clinical trial participants with and without ADAs in the BLV 2 mg and 10 mg groups at Week 24 and Week 48, see table below.

Table 18. Antidrug Antibody to Bulevirtide Summary (Week 24 and Week 48 Full Analysis Sets; studies MYR202[a], MUR203, and MYR301)

	Week 24		Week 48	
	BLV 2 mg (N = 92)	BLV 10 mg (N = 95)	BLV 2 mg (N = 64)	BLV 10 mg (N = 65)
Evaluable for ADA Prevalence	92	95	64	65
ADA Prevalence	21 (22.8%)	20 (21.1%)	18 (28.1%)	17 (26.2%)
ADA Positive at Baseline	6 (6.5%)	3 (3.2%)	3 (4.7%)	3 (4.6%)
ADA Positive Postbaseline	20 (21.7%)	20 (21.1%)	18 (28.1%)	17 (26.2%)
Evaluable for ADA Incidence	92	94	64	64
ADA Incidence	15 (16.3%)	17 (18.1%)	15 (23.4%)	14 (21.9%)
ADA Negative at All Postbaseline Visits But Positive at Baseline	1 (1.1%)	0	0	0

ADA = antidrug antibody; BLV = bulevirtide (GS-4438), formerly known as Myrcludex B (MXB)
[a] Study MYR202 was included in the Week 24 analysis only.
The Week 24 and Week 48 Full Analysis Sets include participants who were randomized and received at least 1 dose of BLV and had at least 1 ADA data point.
The Week 24 and Week 48 evaluable populations for ADA prevalence are participants with at least 1 ADA data point at any visit including baseline.
The Week 24 and Week 48 evaluable populations for ADA incidence are participants with at least 1 ADA data point at postbaseline visits.
ADA prevalence: participants with positive ADA at any visit point in time including baseline are considered ADA positive.
ADA incidence: participants with negative/missing ADA at baseline and at least 1 positive ADA at postbaseline are considered ADA positive.
The percentages are based on the Week 24 and Week 48 evaluable populations, respectively.
There were 12 participants in the Week 24 Full Analysis Set and 5 participants in the Week 48 Full Analysis Set with missing baseline ADA data.

Table 19. HDV RNA Decreased ≥2 log_{10} IU/mL From Baseline or Undetectable HDV RNA Combined With ALT Normalization at Week 24 and Week 48 by ADA Status (Incidence; week 24 and week 48 Full Analysis Sets; Studies MYR202[a], MYR203, and MYR301))

	BLV 2 mg		BLV 10 mg	
	ADA+	ADA−	ADA+	ADA−
Week 24	**(N = 15)**	**(N = 77)**	**(N = 17)**	**(N = 77)**
Responder, n (%)	6 (40.0%)	23 (29.9%)	8 (47.1%)	23 (29.9%)
95% CI	16.3%, 67.7%	20.0%, 41.4%	23.0%, 72.2%	20.0%, 41.4%
Week 48	**(N = 15)**	**(N = 49)**	**(N = 14)**	**(N = 50)**
Responder, n (%)	7 (46.7%)	23 (46.9%)	7 (50.0%)	23 (46.0%)
95% CI	21.3%, 73.4%	32.5%, 61.7%	23.0%, 77.0%	31.8%, 60.7%

ADA = antidrug antibody; ALT = alanine aminotransferase; BLV = bulevirtide (GS-4438), formerly known as Myrcludex B (MXB); HDV = hepatitis D virus; LOD = limit of detection
[a] Study MYR202 was included in the Week 24 analysis only.
Undetectable HDV RNA is HDV RNA less than the LOD. The LOD was 14, 10, and 6 IU/mL in Studies MYR202, MYR203, and MYR301, respectively. The 95% CI was based on Clopper-Pearson exact method.
For Studies MYR202 and MYR203, ALT normalization was defined as ≤ 31 U/L for female participants and ≤ 41 U/L for male participants. For Study MYR301, ALT normalization, as defined by the central laboratories, was ≤ 31 U/L for female participants and ≤ 41 U/L for male participants for Russian sites and ≤ 34 U/L for female participants and ≤ 49 U/L for male participants for all other sites.
For missing values related to coronavirus disease 2019 (COVID-19) in Study MYR301, the last observation carried forward imputation method was used. Otherwise, the missing equals failure imputation method was used.
ADA incidence: participants with negative/missing ADA at baseline and at least 1 positive ADA at postbaseline are considered ADA positive.

Clinical Virology

Resistance testing included sequencing of the N-terminal of PreS1 domain of HBV, covering BLV sequence positions (PreS1 BLV region) , and the HDV HDAg gene. Moreover, there was phenotypic testing of clinical isolates at baseline and Week 24 or Week 48 for participants with virologic breakthrough (VB, defined as 2 consecutive increases in HDV RNA of ≥1 log10 IU/mL from nadir or 2 consecutive HDV RNA values ≥LLOD if previously <LLOD) or non-responders (decline <1 log10 IU/mL). In addition, host NTCP polymorphism analysis was performed for these participants at baseline.

Week 24 Resistance Analysis

Resistance analysis was performed on 8 participants who were non-responders at Week 24 with 6 and 2 participants in the BLV 2 mg and 10 mg groups, respectively. No participants experienced VB at Week 24. No amino acid substitutions at HBV N-terminal of PreS1 domain covering BLV sequence positions (PreS1 BLV region) or HDV HDAg associated with reduced susceptibility to BLV were identified in the isolates from any of these 8 participants at baseline and Week 24.

In the BLV 2 mg group, 6 participants qualified for phenotypic analysis due to less than 1 log10 HDV RNA decline from baseline. At baseline, EC50 data was obtained from 4 of 6 non-responders with EC50 values ranging from 0.31 nM to 0.47 nM. At Week 24, EC50 data was obtained from 3 of 6 non-responders with EC50 values ranging from 0.31 nM to 0.63 nM. Three non-responders had both baseline and Week 24 EC50 values available. Phenotypic analysis of the Week 24 clinical isolates from the 3 participants showed that there were no changes in sensitivity to BLV, with 1.0 − 1.3 fold change range in EC50 values for the Week 24 isolates compared to the corresponding baseline isolates.

In the BLV 10 mg group, 2 participants qualified for phenotypic analysis due to less than 1 log10 HDV RNA decline from baseline. At baseline, EC50 data was obtained from both the 2 non-responders with an EC50 value of 0.38 nM and 0.09 nM respectively. At Week 24, EC50 data was only obtained from 1 non-responder with an EC50 value of 0.55 nM. Phenotypic analysis showed that there was no change in sensitivity to BLV, with a 1.4 fold change in EC50 value for the Week 24 isolate compared to the corresponding baseline isolate

Week 48 Resistance Analysis

Resistance analysis was performed on 11 participants who experienced VB (5 participants) or non-responders (6 participants) at Week 48 with 9 and 2 participants in the BLV 2 mg and 10 mg groups, respectively. No amino acid substitutions at HBV N-terminal of PreS1 domain covering BLV sequence positions (PreS1 BLV region) or HDV HDAg associated with reduced susceptibility to BLV were identified in the isolates from any of these 11 participants at baseline and Week 48 (Table 13 and 14).

Phenotypic analysis of the Week 48 clinical isolates from the 5 participants in the 2 mg arm who qualified for analyses showed that there were no changes in sensitivity to BLV, with 0.8 −1.5 fold change range in EC50 values for the Week 48 isolates compared to the corresponding baseline isolates (Table 13). For the 10 mg arm there was one clinical isolated with a substitution, and there was no change in sensitivity to BLV, with a 1.3 fold change in EC50 value (Table 14).

In addition, 1 baseline NTCP variant detected in 1 non-responder (also non-responder at week 24) was also observed in responders. Another baseline NTCP variant detected in 1 non-responder (also non-responder at week 24) was not at the NTCP binding region, therefore is unlikely to affect BLV binding and the treatment outcomes.

Table 20. Week 48 Sequence Analysis: Change from Baseline HDAg Sequence Results for Participants with Virologic Breakthrough or Non-Responder in the BLV 2 mg Group

Participant	Treatment Arm	WK48 Treatment Response	BL HDV RNA, IU/mL	Week 48 HDV RNA, IU/mL	Changes from BL[a]	Variant EC_{50} (nM)[b]
01-04-302	BLV2mg	Non responder	435000[c]	101665	Unable to sequence[d]	NA
01-04-306	BLV 2mg	Non responder	3091143	6966578	No change from baseline	NA
01-07-318	BLV 2mg	Non responder	64960	9208	F194F/V	No data
04-03-310	BLV 2mg	Non responder	1616474	247030	Unable to sequence[e]	NA
06-01-315	BLV 2mg	Non responder	30390	3614	R124K/R	0.4
01-05-311	BLV 2mg	Virologic Breakthrough	318280	215532	A116S/A A117A/S H121H/Y	S116A (0.37 nM) A117S (0.43 nM) N121H/Y (0.59 nM)
01-06-320	BLV 2mg	Virologic Breakthrough	164185	8180	E46D/E	0.40
04-01-306	BLV 2mg	Virologic Breakthrough	166947	11401	No change from baseline[f]	NA
04-03-317	BLV 2mg	Virologic Breakthrough	56772	28559	G/Y121D/G[f]	0.42

a Changes at any positions in HDAg
b EC_{50} of clinical isolates with substitution
c HDV RNA data at screening was used as the baseline sample was switched and could not be used
d Baseline sequencing was unable to obtain due to baseline sample switch
e Week 48 sequencing was unable to obtain
f Only partial HDAg sequence available for Week 48 sample (aa 1-222)

Table 21. Week 48 Sequence Analysis: Change from Baseline HDAg Sequence Results for Participants with Virologic Breakthrough or Non-Responder in the BLV 10 mg Group

Treatment Arm	WK48 Treatment Response	BL HDV RNA, IU/mL	Week 48 HDV RNA, IU/mL	Changes from BL[a]	Variant BLV EC_{50} (nM)[b]
BLV 10mg	Non responder	1390248	459489	No change from baseline	NA
BLV 10mg	Virologic Breakthrough	604414	7897	K40K/R[c]	0.44

Unable to sequence = either baseline of Week 48 sample or both failed sequencing
a Changes at any positions in HDAg
b EC_{50} of clinical isolates with substitution
c Only partial HDAg sequence available for Week 48 sample (aa 1-109)

The BLV EC50 values from 116 baseline samples from participants showed similar susceptibility to BLV in vitro in participants across different treatment response groups. In the BLV 2 mg treatment arm (non-responder, median EC50=0.42 nM; partial responder, EC50=0.38 nM; responder, EC50=0.27 nM) as well as the 10 mg treatment arm (non-responder, median EC50=0.24 nM; partial responder, EC50=0.41 nM; responder, EC50=0.41 nM). These results showed no differences compared to the delayed treatment group (EC50=0.35 nM).

7.3 Assessor's Discussion – efficacy

Study MYR301 is a Phase 3, randomized, open-label, multicenter, parallel-group study comparing the efficacy and safety of BLV administered as delayed treatment (10 mg/day after 48 weeks) versus immediate treatment (2 mg or 10 mg/day) for the treatment of CHD for 144 weeks. A total of 150 participants were randomized (delayed treatment group: 51 participants; BLV 2 mg treatment group: 49 participants; BLV 10 mg treatment group: 50 participants). Of the 99 participants randomized and treated with BLV, 4 participants discontinued the study prior to the Week 48 data cutoff date, due to withdrawal of consent (n=3) and physician decision (n=1). Interim results after 48 weeks are presented.

Superiority of BLV treatment vs. delayed treatment was demonstrated at 48 weeks in that 42.9% in 2 mg BLV treatment group and in 48.0% in the 10 mg group achieved the primary efficacy endpoint (undetectable HDV RNA or decrease in HDV RNA by ≥ 2 $\log_{10}$ IU/mL from baseline and ALT normalization) compared to only 2 % in the delayed treatment group. The key secondary endpoint "the proportion of participants with undetectable HDV RNA" was not statistically significant between the 2 mg (12.2%) and 10 mg (20.0%) BLV treatment groups. However, a difference is noted compared to the participants in the delayed treatment group where none achieved the secondary endpoint.

Additional secondary endpoints were explorative. More patients with ALT normalisation, changes in liver stiffness and HDV RNA decrease by ≥ 2 $\log_{10}$ IU/mL from baseline were observed in both treatment groups compared to the delayed treatment arm. Subgroup analyses on cirrhotic patients indicated a treatment effect of BLV. A numerically larger proportion of cirrhotic patients achieved the primary endpoint in the 10 mg BLV treatment group compared to the 2 mg BLV group, implying a dose dependent increase in efficacy.

The MAH has provided integrated clinical immunogenicity data which was also assessed as part of the latest PSUSA (period 31 January 2022 to 30 July 2022). It is agreed that there were no meaningful differences in efficacy endpoints (combined response, viral response, and ALT normalization) between clinical trial participants with and without ADAs in the BLV 2 mg and 10 mg groups at Week 24 and Week 48. The Hepcludex EU SmPC has been updated with a statement related to immunogenicity and ADA prevalence in Section 5.1 of the SmPC which is endorsed.

Resistance analysis showed that patients who experienced virological breakthrough at 48 weeks did not have PreS1 BLV region or HDAg amino acid substitutions, neither at baseline nor at week 48. Phenotyping at week 24 and 48 demonstrated that the clinical isolates tested remained sensitive to BLV. In addition, the BLV EC50 values from baseline samples were similar across non-responders, participants with VB, partial responders and virologic responders.

Off-treatment durability of virological responses remain to be evaluated.

Sample switches were detected by the MAH during resistance analysis week 48 and therefore other possible switches were evaluated by assessment of individual participant HDV RNA vs time curves and bi-directional viral blips, defined as any fluctuation of > 2 log10 from the preceding and subsequent timepoints for all participants in Study MYR301. Additional sequencing and phylogenetic analyses were undertaken, and a total of 8 participants (4 pairs) were identified as having switched samples.

Once the issue was discovered all participants samples were evaluated for potential switches. No additional switches were identified which is reassuring and the approach used seems appropriate.

The MAH performed audits at the responsible sites. Most likely the switches occurred during blood draw because quality control checks were not properly followed at the impacted sites. The switched or compromised samples were from three different sites in Russia and one in Germany. All of the Study MYR301 sites were retrained on bio-sample management as part of the immediate corrective action. It is acknowledged that switches most likely occurred due to inadequate training of site staff.

The MAH claimed the effect on other laboratory values other than HDV-RNA is minimal. Analytes that were included in the same kits as the impacted samples were considered as probable switches and treated as missing data, this corrective action is supported. Different processes were in place for safety samples which were analysed on the same day for real time ongoing safety assessments. The MAH has conducted a review of the impacted participants samples (hematology parameters, serum chemistries, including alanine aminotransferase levels, and total bile salt levels) and this analysis did not indicate that switching of safety samples had occurred.

Overall, the actions taken by the MAH seem sufficient to ensure no additional samples were switched and the MAH will proactively assess for potential switches in subsequent analyses of participants in the study. It is agreed that the interpretation of the results from Study MYR301 remains unchanged**.**

The MAH has suggested to update section 5.1 in the SmPC which was endorsed with adjustments as specified in the product information sections of the AR and the SmPC. In general, only type I error-controlled data should constitute claims regarding the product performance. The MAH suggested including a claim regarding liver stiffness in the SmPC Section 5.1. However, the observed decrease in LSM with BLV treatment seem to more likely be due to decreased necroinflammation than improved/stable fibrosis. As the LSM data is only of exploratory nature and the evidence for a notable impact on fibrosis is weak, including these data in the SmPC is not supported.

Data confirm the efficacy of BLV as well as the selection of the 2 mg dose.

The benefit remains positive.

8. Clinical Safety aspects

8.1. Methods – analysis of data submitted

Sources of Data Supporting the Clinical Safety of Bulevirtide

The safety analysis consists of on-treatment Week 48 safety data from the ongoing Study MYR301 (Table 1). Supportive pooled safety data analysis from Week 48 of the Phase 2 Study MYR203 and the Phase 3 Study MYR301 are also included to support the proposed presentation of adverse drug reactions (ADRs) and their frequencies in the EU summary of product characteristics (SmPC) updates.

An overview of the MYR301 Week 48 safety data is presented by randomized treatment group. In addition, the safety data from the pooled clinical studies were utilized to revise frequencies of adverse events (AEs) considered to be adverse drug reactions (ADRs) or laboratory abnormalities associated with BLV treatment.

Table 22. Overview of Primary Studies/Programs Providing Safety Data for Bulevirtide

Study	Study Design	Treatment Regimens	Number of Participants[a] by Treatment Regimen	Participant Population and Data Presented	Location of Study Narrative and Report
MYR301	Phase 3, randomized, open-label, multicenter, parallel-group study comparing the efficacy and safety of immediate and ongoing treatment with BLV (2 mg or 10 mg/day) versus	Treatment Group A: Delayed treatment with BLV 10 mg/day for 96 weeks Treatment Group B: Immediate treatment with BLV 2 mg/day for 144 weeks Treatment Group C: Immediate	Randomized: 150 Delayed treatment: 51 BLV 2 mg: 49 BLV 10 mg: 50	Adults aged 18-65 years (inclusive); Positive PCR results for serum/plasma HDV RNA; ALT level > 1 × ULN but < 10 × ULN; serum	m2.7.3, Section 2 MYR301 Interim Week 24 CSR MYR301 Interim Week 48 CSR (Revision)

Study	Study Design	Treatment Regimens	Number of Participants[a] by Treatment Regimen	Participant Population and Data Presented	Location of Study Narrative and Report
	a delay of 48 weeks followed by BLV 10 mg/day after 48 weeks for the treatment of CHD.	treatment with BLV 10 mg/day for 144 weeks		albumin > 28 g/L, with or without compensated liver cirrhosis; Child-Pugh score ≤ 7. Week 48 safety data	

ALT = alanine aminotransferase; BLV = bulevirtide (GS-4438), formerly known as Myrcludex B; CHD = chronic hepatitis delta infection; CSR = clinical study report; HDV = hepatitis delta virus; PCR = polymerase chain reaction; ULN = upper limit of normal

1) Participants who received at least 1 dose of study treatment.

Analysis of Adverse Events

All AEs presented were treatment-emergent and are referred to as AEs throughout this document. Additionally, the relationship of AEs to study treatments and severity of AEs was investigator assigned.

Study MYR301 AEs, serious adverse events (SAEs), AEs leading to study drug discontinuation, and AEs of interest are summarized below.

For AEs that were considered to be ADRs or laboratory abnormalities to BLV, on-treatment Week 48 safety data from Study MYR301 were pooled with on-treatment Week 48 safety data from Study MYR203 to align with the proposed EU SmPC updates.

8.2. Results

Overall Extent of Exposure

The safety profile of BLV presented in this summary for Study MYR301 is based on data from 150 participants who received at least 1 dose of study drug (BLV 2 mg treatment group: 49 participants; BLV 10 mg treatment group: 50 participants) or randomized to delayed treatment group (51 participants)

The mean (SD) duration of exposure to study drug in Study MYR301 was similar between the 2 BLV treatment groups: 47.90 (0.38) weeks (for BLV 2 mg) and 45.75 (8.83) weeks (for BLV 10 mg).

Adverse events

Overall Summary of Adverse Events

Table 23 provides an overall summary of AEs by treatment group in Study MYR301 up to Week 48. The percentages of participants in each treatment group who experienced at least 1 AE were similar across the treatment groups.

The majority of AEs considered related to study drug by the investigator were Grade 1 or 2 in severity. Few participants had Grade 3 AEs considered related to study drug (BLV 2 mg treatment group: 2.0%, 1 participant; BLV 10 mg treatment group: 6.0%, 3 participants); there were no participants who experienced a Grade 4 AE. Frequencies of Grade 3 or 4 AEs were similar across all treatment groups

(delayed treatment group: 5.9%, 3 participants; BLV 2 mg treatment group: 10.2%, 5 participants; BLV 10 mg treatment group: 8.0%, 4 participants).

Serious adverse events were similar across treatment groups (delayed treatment group: 2.0%, 1 participant; BLV 2 mg treatment group: 4.1%, 2 participants; BLV 10 mg treatment group: 2.0%, 1 participant), and none were considered related to BLV. No participants discontinued study drug due to AEs and no deaths were reported.

Table 23. MYR301: Overall Summary of Adverse Events During the First 48 Weeks (Safety Analysis Set)

	Delayed Treatment (N = 51)	**BLV 2 mg (N = 49)**	**BLV 10 mg (N = 50)**
TEAE	39 (76.5%)	40 (81.6%)	44 (88.0%)
TEAE With Grade 3 or Higher	3 (5.9%)	5 (10.2%)	4 (8.0%)
TEAE With Grade 2 or Higher	12 (23.5%)	23 (46.9%)	27 (54.0%)
TEAE Related to Study Drug	0	24 (49.0%)	36 (72.0%)
TEAE Related to Study Drug With Grade 3 or Higher	0	1 (2.0%)	3 (6.0%)
TEAE Related to Study Drug With Grade 2 or Higher	0	10 (20.4%)	16 (32.0%)
TE Serious AE	1 (2.0%)	2 (4.1%)	1 (2.0%)
TE Serious AE Related to Study Drug	0	0	0
TEAE Leading to Premature Discontinuation of Study Drug	0	0	0
Death	0	0	0

AE = adverse event; BLV = bulevirtide (GS-4438), formerly known as Myrcludex B; TE = treatment emergent; TEAE = treatment-emergent adverse event
Adverse events were coded according to MedDRA Version 24.0. Treatment-emergent events began on or after the study drug start date up to 30 days after permanent discontinuation of study drug or led to premature study drug discontinuation. For delayed treatment group, treatment-emergent events began on or after the randomization date up to the Week 48 visit date, or up to study discontinuation date if discontinued study before the Week 48 visit.
Severity grades were defined by the Common Terminology Criteria for Adverse Events Version 5.0.
Death includes any death that occurred during the study.

Common Adverse Events

AEs observed in ≥ 5% of participants

Table 24 presents a summary of AEs experienced by ≥ 5% of participants in any treatment group in Study MYR301 through Week 48. The most commonly reported AEs by treatment group were as follows:

- Delayed treatment group: leukopenia (17.6%, 9 participants), thrombocytopenia and vitamin D deficiency (15.7%, 8 participants each), and lymphopenia (7.8%, 4 participants)
- BLV 2 mg treatment group: headache (18.4%, 9 participants), leukopenia, vitamin D deficiency, and pruritus (12.2%, 6 participants each), and thrombocytopenia, eosinophilia, and fatigue (10.2%, 5 participants each)
- BLV 10 mg treatment group: headache (20.0%, 10 participants), vitamin D deficiency and pruritus (16.0%, 8 participants each), fatigue (14.0%, 7 participants), and abdominal pain upper (12.0%, 6 participants)

Table 24. MYR301: Adverse Events in ≥ 5% of Participants in Any Treatment Group (Safety Analysis Set)

Adverse Event by System Organ Class and Preferred Term	**Delayed Treatment (N = 51)**	**BLV 2 mg (N = 49)**	**BLV 10 mg (N = 50)**
Number of participants experiencing any treatment-emergent AE	39 (76.5%)	40 (81.6%)	44 (88.0%)
Blood and lymphatic system disorders	15 (29.4%)	17 (34.7%)	15 (30.0%)
Leukopenia	9 (17.6%)	6 (12.2%)	5 (10.0%)
Thrombocytopenia	8 (15.7%)	5 (10.2%)	5 (10.0%)

Adverse Event by System Organ Class and Preferred Term	Delayed Treatment (N = 51)	BLV 2 mg (N = 49)	BLV 10 mg (N = 50)
Lymphopenia	4 (7.8%)	3 (6.1%)	4 (8.0%)
Eosinophilia	0	5 (10.2%)	5 (10.0%)
Neutropenia	3 (5.9%)	2 (4.1%)	5 (10.0%)
Anaemia	3 (5.9%)	3 (6.1%)	2 (4.0%)
Cardiac disorders	2 (3.9%)	1 (2.0%)	6 (12.0%)[a]
Bradycardia	0	0	3 (6.0%)
Gastrointestinal disorders	4 (7.8%)	8 (16.3%)	14 (28.0%)
Nausea	2 (3.9%)	3 (6.1%)	4 (8.0%)
Abdominal pain upper	1 (2.0%)	0	6 (12.0%)
Abdominal pain	1 (2.0%)	1 (2.0%)	3 (6.0%)
General disorders and administration site conditions	2 (3.9%)	14 (28.6%)	23 (46.0%)
Fatigue	1 (2.0%)	5 (10.2%)	7 (14.0%)
Injection site reaction	0	3 (6.1%)	4 (8.0%)
Injection site erythema	0	2 (4.1%)	4 (8.0%)
Asthenia	0	2 (4.1%)	3 (6.0%)
Injection site pruritus	0	1 (2.0%)	3 (6.0%)
Injection site swelling	0	1 (2.0%)	3 (6.0%)
Infections and infestations	13 (25.5%)	11 (22.4%)	11 (22.0%)
Nasopharyngitis	2 (3.9%)	4 (8.2%)	0
Investigations	8 (15.7%)	11 (22.4%)	11 (22.0%)
Alanine aminotransferase increased	3 (5.9%)	2 (4.1%)	3 (6.0%)
Aspartate aminotransferase increased	3 (5.9%)	1 (2.0%)	1 (2.0%)
Total bile acids increased	0	1 (2.0%)	3 (6.0%)
Metabolism and nutrition disorders	9 (17.6%)	8 (16.3%)	9 (18.0%)
Vitamin D deficiency	8 (15.7%)	6 (12.2%)	8 (16.0%)
Musculoskeletal and connective tissue disorders	1 (2.0%)	7 (14.3%)	8 (16.0%)
Arthralgia	0	3 (6.1%)	4 (8.0%)
Nervous system disorders	0	11 (22.4%)	13 (26.0%)
Headache	0	9 (18.4%)	10 (20.0%)
Psychiatric disorders	2 (3.9%)	1 (2.0%)	5 (10.0%)
Sleep disorder	1 (2.0%)	0	3 (6.0%)
Renal and urinary disorders	3 (5.9%)	4 (8.2%)	5 (10.0%)
Proteinuria	2 (3.9%)	3 (6.1%)	1 (2.0%)
Skin and subcutaneous tissue disorders	1 (2.0%)	9 (18.4%)	12 (24.0%)
Pruritus	0	6 (12.2%)	8 (16.0%)
Vascular disorders	1 (2.0%)	2 (4.1%)	4 (8.0%)
Hypertension	0	1 (2.0%)	3 (6.0%)

AE = adverse event; BLV = bulevirtide (GS-4438), formerly known as Myrcludex B; PT = preferred term; SOC = system organ class

a In the BLV 10 mg group, the following nonbradycardia cardiac AEs occurred in 1 participant (2.0%) each: angina pectoris, atrioventricular block first degree, and tachycardia.

Adverse events were coded according to MedDRA Version 24.0.

Treatment-emergent events began on or after the study drug start date up to 30 days after permanent discontinuation of study drug or led to premature study drug discontinuation. For delayed treatment group, treatment-emergent events began on or after the randomization date up to the Week 48 visit date, or up to study discontinuation date if discontinued study before the Week 48 visit.

Multiple AEs were counted only once per participants for the highest severity grade for each SOC and PT.

System organ classes were presented alphabetically, and PTs within SOC were presented by descending order of the total frequencies.

Source: MYR301 Interim Week 48 CSR (Revision), Table 31

AEs observed in ≥ 10% of participants

The following AEs were observed in ≥ 10% of participants and occurred more frequently in the BLV 2 mg and 10 mg treatment groups than in the delayed treatment group; all are considered ADRs (fatigue, injection site reactions, headache, pruritus) or laboratory abnormalities (eosinophilia) associated with BLV treatment:

Eosinophilia: 10.2% (5 participants) in the BLV 2 mg treatment group and 10.0% (5 participants) in the BLV 10 mg treatment group versus 0 in the delayed treatment group

Fatigue: 10.2% (5 participants) in the BLV 2 mg treatment group and 14.0% (7 participants) in the BLV 10 mg treatment group versus 2.0% (1 participant) in the delayed treatment group

Injection site reactions: 16.3% (8 participants) in the BLV 2 mg treatment group and 30.0% (15 participants) in the BLV 10 mg treatment group (based on AEs under the MedDRA high-level term [HLT] "injection site reactions") versus 0 in the delayed treatment group (note: this group received no injections of study drug).

Headache: 18.4% (9 participants) in the BLV 2 mg treatment group and 20.0% (10 participants) in the BLV 10 mg treatment group versus 0 in the delayed treatment group

Pruritus: 12.2% (6 participants) in the BLV 2 mg treatment group and 16.0% (8 participants) in the BLV 10 mg treatment group versus 0 in the delayed treatment group); pruritus is described further in Section 0.

The frequencies and types of AEs were similar in both the BLV 2 mg and 10 mg treatment groups, with the exception of the AEs with the HLT "injection site reactions" (ie, injection site reaction, erythema, pruritus, swelling), which were reported more frequently in participants randomized to the BLV 10 mg treatment group than those in the BLV 2 mg treatment group.

Adverse Events from Pooled Safety Data Analysis of Studies MYR203 and MYR301 Compared With Adverse Events in Study MYR301

Table 25 presents a summary of 'very common' AEs (experienced by ≥ 10% of participants) in any treatment group in the pooled data from Studies MYR203 (Week 48) and MYR301 (Week 48).

The following AEs were observed very commonly (in ≥ 10% of participants) in either or both Study MYR301 Week 48 analysis and the pooled analysis of safety data and had an increased frequency in the BLV groups compared with the delayed treatment group; all considered to be ADRs to BLV.

Headache: BLV 2 mg treatment group: 18.4% (9 participants) in Study MYR301 and 15.6% (10 participants) in the pooled data; BLV 10 mg treatment group: 20.0% (10 participants) in Study MYR301 and 18.5% (12 participants) in the pooled data

Injection site reactions: BLV 2 mg treatment group: 16.3% (8 participants) in Study MYR301 and 15.6% (10 participants) in the pooled data; BLV 10 mg treatment group: 30.0% (15 participants) in Study MYR301 and 27.7% (18 participants) in the pooled data (Section 0)

Pruritus: BLV 2 mg treatment group: 12.2% (6 participants) in Study MYR301 and 10.9% (7 participants) in the pooled data; BLV 10 mg treatment group: 16.0% (8 participants) in Study MYR301 and 12.3% (8 participants) in the pooled data

Eosinophilia: BLV 2 mg treatment group: 10.2% (5 participants) in Study MYR301 and 9.4% (6 participants) in the pooled data; BLV 10 mg treatment group: 10.0% (5 participants) in Study MYR301 and 7.7% (5 participants) in the pooled data (Section 0)

Fatigue: BLV 2 mg treatment group: 10.2% (5 participants) in Study MYR301 and 9.4% (6 participants) in the pooled data; BLV 10 mg treatment group: 14.0% (7 participants) in Study MYR301 and 10.8% (7 participants) in the pooled data.

*Total bile acids increased**: BLV 2 mg treatment group: 2.0% (1 participant) in Study MYR301 and 18.8% (12 participants) in the pooled data; BLV 10 mg treatment group: 6.0% (3 participants) in Study MYR301 and 27.7% (18 participants) in the pooled data

* Note, the reporting of AEs associated with total bile salt elevations was carried out differently across the studies: in Study MYR203, elevations were reported by the investigator as AEs related to study treatment; in Study MYR301, only bile salt elevations that were symptomatic or judged by the investigator to be clinically significant were reported as AEs. This change in protocol-specified reporting accounts for the difference in frequency of the AE of total bile acids increased in Study MYR301.

Table 25. MYR203 and MYR301: Adverse Events in ≥ 10% of Participants in Any Treatment Group (Safety Analysis Set)

Adverse Event by System Organ Class and Preferred Term	**Delayed Treatment (N = 51)**	**BLV 2 mg (N = 64)**	**BLV 10 mg (N = 65)**
Number of participants experiencing any treatment-emergent AE by Week 48	39 (76.5%)	54 (84.4%)	59 (90.8%)
Blood and lymphatic system disorders	15 (29.4%)	24 (37.5%)	25 (38.5%)
Thrombocytopenia	8 (15.7%)	8 (12.5%)	10 (15.4%)
Leukopenia	9 (17.6%)	9 (14.1%)	9 (13.8%)
Neutropenia	3 (5.9%)	5 (7.8%)	8 (12.3%)
General disorders and administration site conditions	2 (3.9%)	18 (28.1%)	26 (40.0%)
Fatigue	1 (2.0%)	6 (9.4%)	7 (10.8%)
Investigations	8 (15.7%)	23 (35.9%)	26 (40.0%)
Total bile acids increased	0	12 (18.8%)	18 (27.7%)
Alanine aminotransferase increased	3 (5.9%)	4 (6.3%)	7 (10.8%)
Metabolism and nutrition disorders	9 (17.6%)	8 (12.5%)	12 (18.5%)
Vitamin D deficiency	8 (15.7%)	6 (9.4%)	8 (12.3%)
Nervous system disorders	0	14 (21.9%)	15 (23.1%)
Headache	0	10 (15.6%)	12 (18.5%)
Skin and subcutaneous disorders	1 (2.0%)	11 (17.2%)	13 (20.0%)
Pruritus	0	7 (10.9%)	8 (12.3%)

AE = adverse event; BLV = bulevirtide (GS-4438), formerly known as Myrcludex B; PT = preferred term; SOC = system organ class
Adverse events were coded according to MedDRA Version 24.0.
Treatment-emergent events began on or after the study drug start date up to 30 days after permanent discontinuation of study drug, or led to premature study drug discontinuation. For delayed treatment group in Study MYR301, treatment-emergent events began on or after the randomization date up to Week 48 visit date, or up to the discontinuation date if participants discontinued before Week 48.
Multiple AEs were counted only once per participant for the highest severity grade for each SOC and PT.
SOCs were presented alphabetically and PTs within SOC were presented by descending order of the total column.
For Study MYR301, only symptomatic bile acids increase cases were collected.

Other Adverse Events of Interest

Hepatic Safety

All Hepatic AEs were Grade 1 or 2 in severity, and none resulted in discontinuation of study drug.

In Study MYR301, the Hepatic AEs by treatment group were as follows; all observed events had a frequency of < 10%:

- Delayed treatment group: alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased (5.9%, 3 participants each); gamma-glutamyltransferase increased (2.0%, 1 participant)

- BLV 2 mg treatment group: ALT increased, hyperbilirubinemia, blood bilirubin increased (4.1%, 2 participants each); AST increased, hepatic pain (2.0%, 1 participant each)

- BLV 10 mg treatment group: ALT increased (6.0%, 3 participants); hyperbilirubinemia, gamma-glutamyltransferase increased (4.0%, 2 participants each); AST increased, blood bilirubin increased, hepatic pain (2.0%, 1 participant each)

To evaluate the potential for liver toxicity with BLV, an analysis of potential drug-induced liver injury (DILI) based on the principles of Hy's Law was performed using the following 3 laboratory-based criteria: ALT and/or AST > 3 × upper limit of normal (ULN) and total bilirubin > 2 × ULN; ALT > 5 × ULN; and total bilirubin > 2 × ULN. Given that all the participants in this analysis have an underlying liver disease, these criteria provide a conservative evaluation of the potential for liver toxicity, according to the MAH.

Participants who met the criteria only at baseline were excluded from the analyses as these events were not considered treatment emergent. In the BLV treatment groups, 11.1% (11 of 99) of participants met the specified laboratory-based criteria while on treatment: 6 participants in the BLV 2 mg treatment group and 5 participants in the BLV 10 mg treatment group (compared with 19.6% [10 of 51] of participants in the delayed treatment group). None of these events were considered to meet criteria for Hy's Law cases due to potential alternative etiologies from underlying HDV infection and medical history.

An external Hepatic Safety Adjudication Committee (HSAC) was implemented to assess all severe and serious AEs related to the hepatobiliary system and other significant safety issues as considered necessary by the sponsor. The HSAC independent review of these cases of potential DILI concurred with the assessment that none of these cases are consistent with BLV-induced liver injury.

In the pooled analyses of safety data, on-treatment hepatic events were observed at similar frequencies to Study MYR301 for the BLV 2 mg and BLV 10 mg treatment groups.

Eosinophilia

Both AEs and laboratory abnormalities associated with eosinophilia are described below.

In Study MYR301, the AEs of eosinophilia and eosinophil count increased by treatment group were as follows:

- Delayed treatment group: eosinophil count increased (2.0%, 1 participant)

- BLV 2 mg treatment group: eosinophilia (10.2%, 5 participants)

- BLV 10 mg treatment group: eosinophilia (10.0%, 5 participants) and eosinophil count increased (2.0%, 1 participant)

All eosinophilia AEs were Grade 1 in severity, and none resulted in discontinuation of study drug or interruption of study treatment. The eosinophilia AEs were considered related to study drug for 8.2% (4 of 49) of participants in the BLV 2 mg treatment group and 6.0% (3 of 50) of participants in the BLV 10 mg

treatment group. The AE of eosinophil count increased was considered by the investigator to be related to study drug only for 1 participant (2.0%) in the BLV 10 mg treatment group. Overall, the frequency of AEs of eosinophilia and eosinophil count increased were comparable for participants treated with BLV 2 mg and BLV 10 mg. Of the events considered related to study drug by the investigator, 1 participant had a hepatic AE of GGT increased, which was concurrent with eosinophil count increased.

In the pooled analysis of safety data from Studies MYR203 and MYR301, the AEs of eosinophilia and eosinophil count increased by treatment group were as follows:

- Delayed treatment group: eosinophil count increased (2.0%, 1 participant)
- BLV 2 mg treatment group: eosinophilia (9.4%, 6 participants)
- BLV 10 mg treatment group: eosinophilia (7.7%, 5 participants) and eosinophil count increased (1.5%, 1 participant)

Given these results, the frequency of eosinophilia in participants receiving BLV 2 mg in the pooled data was categorized as common (1 to < 10% of participants).

Laboratory Abnormalities

Six participants (2 participants in the BLV 2 mg and 4 participants in the BLV 10 mg treatment groups) experienced persistent elevation of absolute eosinophils above ULN on ≥ 2 consecutive visits. The elevations in eosinophils were generally transient and resolved with ongoing BLV treatment.

Eosinophil Laboratory Abnormalities and Analysis for Potential Association with DILI

Although eosinophilia can be indicative of DILI, none of the 6 participants who experienced persistent elevation of absolute eosinophils (defined above) met the laboratory-based criteria for potential DILI. However, 1 of the 6 participants in the BLV 10 mg treatment group who experienced persistently elevated eosinophil counts had a nonconcurrent hepatic AE of blood bilirubin increased (there was a potential alternative etiology to the event: the participant had underlying cirrhosis and had ongoing chronic pancreatitis and chronic cholecystitis, both of which are known to cause elevations in serum bilirubin).

Injection Site Reactions

Across the BLV development program, participants randomized to the BLV 10 mg treatment group were required to administer 2 injections of BLV 5 mg given daily, compared with 1 injection daily for the BLV 2 mg treatment group.

In Study MYR301, injection site reactions were evaluated using the HLT of "injection site reactions"; additionally, local reactions at the injection site were evaluated by the investigator according to the table for clinical abnormalities from "Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials.

In Study MYR301, AEs in the HLT "injection site reactions" occurred very commonly (ie, in ≥ 10% of participants) in the BLV-containing treatment groups, with higher frequencies seen in the BLV 10 mg treatment group (30.0%, 15 participants) than in the BLV 2 mg treatment group (16.3%, 8 participants). This is likely due to the higher daily injection burden in the BLV 10 mg treatment group (2 daily injections versus 1 daily injection).

All but 2 of the observed local reactions at injection sites were of mild intensity (2 participants in the BLV 10 mg treatment group had moderate erythema/redness).

In the pooled analyses of safety data, injection site reactions were analyzed using the same approach as in Study MYR301, utilizing the HLT "injection site reactions." Injection site reactions in the pooled clinical study data were also very commonly observed (ie, in ≥ 10% participants) in both of the BLV-containing groups. Frequencies of injection site reactions in the pooled data were higher in the BLV 10 mg treatment group (27.7%, 18 participants) than in the BLV 2 mg treatment group (15.6%, 10 participants).

The injection site reaction AEs by BLV treatment group and delayed treatment in Study MYR301 and in the pooled data are presented in (Table 26. As there were no study drug injections for participants in the delayed treatment group through Week 48, no injection site reaction occurred in this group (Table 26).

MYR301 and Pooled Data (MYR203 and MYR301): Injection Site Reactions (Safety Analysis Set)

	Study MYR301			**Pooled Data**		
Preferred Term	**Delayed treatment (N = 51)**	**BLV 2 mg (N = 49)**	**BLV 10 mg (N = 50)**	**Delayed Treatment (N = 51)**	**BLV 2 mg (N = 64)**	**BLV 10 mg (N = 65)**
Number (%) of participants with any treatment-emergent adverse event of injection site reactions by Week 48	0	8 (16.3%)	15 (30.0%)	0	10 (15.6%)	18 (27.7%)
Injection site erythema	0	2 (4.1%)	4 (8.0%)	0	3 (4.7%)	5 (7.7%)
Injection site reaction	0	3 (6.1%)	4 (8.0%)	0	3 (4.7%)	5 (7.7%)
Injection site pruritus	0	1 (2.0%)	3 (6.0%)	0	1 (1.6%)	4 (6.2%)
Injection site haematoma	0	1 (2.0%)	2 (4.0%)	0	1 (1.6%)	2 (3.1%)
Injection site swelling	0	1 (2.0%)	3 (6.0%)	0	1 (1.6%)	3 (4.6%)
Injection site pain	0	2 (4.1%)	1 (2.0%)	0	2 (3.1%)	1 (1.5%)
Injection site rash	0	0	2 (4.0%)	0	0	2 (3.1%)
Injection site dermatitis	0	0	1 (2.0%)	0	0	1 (1.5%)
Injection site induration	0	0	0	0	1 (1.6%)	0
Injection site irritation	0	0	1 (2.0%)	0	0	1 (1.5%)

AE = adverse event; BLV = bulevirtide (GS-4438), formerly known as Myrcludex B; PT = preferred term
Adverse events were coded according to MedDRA Version 24.0.
Treatment-emergent events began on or after the study drug start date up to 30 days after permanent discontinuation of study drug, or led to premature study drug discontinuation. For delayed treatment group in Study MYR301, treatment-emergent events began or worsened after the randomization date up to Week 48 visit date, or up to the discontinuation date if participants discontinued before Week 48.
Multiple AEs were counted only once per participant for the highest severity grade for each PT.
PTs were presented by descending order of the total column.
Source: MYR301 Interim Week 48 CSR (Revision), Section 11.3.4.3 and Bulevirtide Week 48 ISS Ad Hoc Table 11044.1

Hypersensitivity, Angioedema, and Anaphylactic/Anaphylactoid Responses

In Study MYR301, no participants experienced an anaphylactic reaction or anaphylactoid response or had an AE of hypersensitivity. One participant in the BLV 2 mg treatment group experienced an AE of angioedema on Day 109 that was nonserious, Grade 2 in severity, and not considered related to BLV therapy.

In the pooled analyses of safety data, one participant experienced an AE of angioedema in the BLV 2 mg treatment group (from Study MYR301). No participants experienced an AE of hypersensitivity, anaphylactic reaction or anaphylactoid response.

Skin and Subcutaneous Disorders

In Study MYR301, skin and subcutaneous disorder AEs were experienced by a similar percentage of participants in the BLV 2 mg and BLV 10 mg treatment groups (BLV 2 mg treatment group: 18.4%, 9 participants; BLV 10 mg treatment group: 24.0%, 12 participants), but were only experienced by 1 participant in the delayed treatment group (2.0%, 1 participant). All skin and subcutaneous disorder AEs were Grade 1 or 2 in severity, and none resulted in discontinuation of study drug.

The frequency of pruritus in Study MYR301 was 12.2% (6 participants) in the BLV 2 mg group, 16.0% (8 participants) in the 10 mg group, versus 0 participants in the delayed treatment group. Therefore, the frequency of pruritus was assessed to be very common (≥ 10% of participants) in Study MYR301.

In the pooled analyses of safety data, pruritus was observed at a frequency of 10.9% (7 participants) in the BLV 2 mg group, 12.3% (8 participants) in the BLV 10 mg group, versus 0 participants in the delayed treatment group. Therefore, the frequency of pruritus in the pooled data was categorized as very common (≥ 10% of participants).

Increased Bile Salts

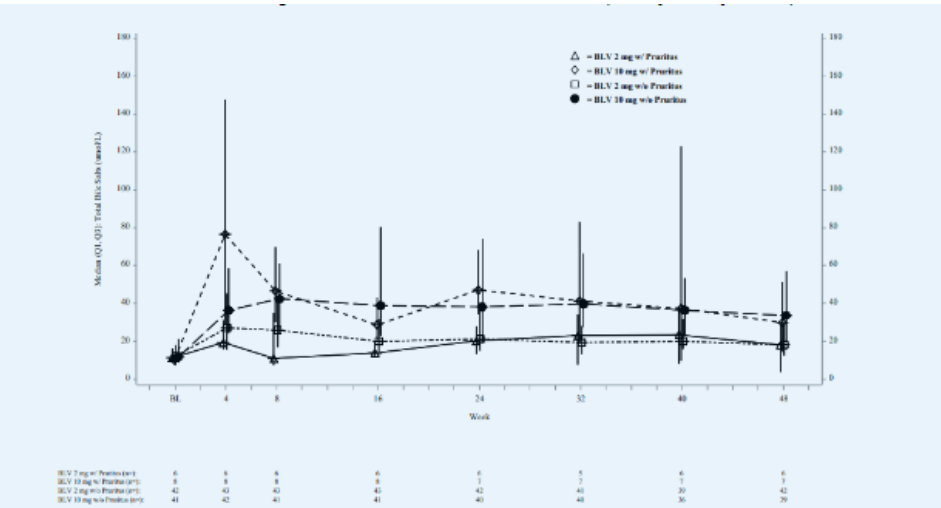
Bile salt elevations are expected given the known mechanism of action of BLV that inhibits NTCP, a bile acid transporter contained within hepatocytes. In accordance with the MYR301 study protocol, if an isolated increase of total bile salts above the ULN was both asymptomatic and judged by the investigator to be clinically insignificant, it was not reported as an AE, which was the case for the vast majority of bile salt increases during 48 weeks.

In Study MYR301, the vast majority of bile salt increases were not reported as AEs. Those reported as AEs were asymptomatic but considered clinically significant by the investigator. The frequencies of the AE of total bile acids increased were low for both of the BLV treatment groups, but were numerically higher in the BLV 10 mg treatment group than the BLV 2 mg treatment group (BLV 2 mg treatment group: 2.0%, 1 participant; BLV 10 mg treatment group: 6.0%, 3 participants).

In the pooled analyses of safety data, the frequency of the AE of total bile acids increased was 18.8% (12 participants) in the BLV 2 mg treatment group and 27.7% (18 participants) in the BLV 10 mg group. Note that the frequency in the pooled data is higher than in Study MYR301, due to the difference in reporting of AEs associated with bile salt elevations in the different studies (Section 0). Given this, the frequency of total bile acids increased in the pooled data was categorized as very common (≥ 10%).

Bile Salts and Pruritus

To assess the possible impact of elevated bile salts associated with BLV treatment on the development of pruritus, an ad hoc analysis was performed for participants in MYR301. There did not appear to be a clear correlation between the presence of pruritus and the levels of bile salts in either the BLV 2 mg or BLV 10 mg treatment group (***Figure 2***).



BL = baseline; BLV = bulevirtide (GS-4438), formerly known as Myrcludex B (MXB); Q1 = first quartile; Q3 = third quartile
Baseline value was the last available value collected prior to first dose of study drug.
Source: Section 15.1, Ad Hoc Figure 10974.1

Figure 2. MYR301: Total Bile Salts (µmol/L) (Median [Q1,Q3]) Over Time for Participants With and Without Pruritus (Safety Analysis Set)

Liver-related clinical events

One liver-related clinical event (bleeding from esophageal varices) was reported in 1 participant (2.0%) in the delayed treatment group, and 1 planned liver-related hospitalization not associated with any AE was reported in 1 participant (2.0%) in the BLV 2 mg treatment group.

Antidrug Antibody (ADA)–Positivity Versus –Negativity

A participant was defined as ADA-positive if at least 1 postbaseline sample was positive and was defined as ADA-negative if all postbaseline samples were negative for the confirmatory assay. Overall, there were fewer BLV-treated participants in the ADA-positive subgroup (20.2%, 20 of 99 participants) than BLV-treated participants in the ADA-negative subgroup (78.8%, 78 of 99 participants)

The most commonly reported AE in the ADA-positive subgroups in both the BLV 2 mg and 10 mg treatment groups was injection site reactions. The same was true for the ADA-negative subgroups.

Antidrug antibody–positive participants generally had either similar or less frequent events across the majority of preferred terms than ADA-negative participants in the BLV treatment groups. However, interpretation of the significance of any differences in individual AEs between ADA-positive versus ADA-negative is limited due to small numbers of events and the differences in sample sizes within the BLV 2 mg and 10 mg treatment groups.

Renal Safety

Overall, the frequencies of AEs of renal and urinary disorders were low across all treatment groups in Study MYR301. During the 48-week period, there were no clinically relevant changes from baseline within

groups or differences between BLV 2 mg and BLV 10 mg in pH, specific gravity, erythrocytes, leukocytes, and nitrite parameters measured during urinalysis.

8.3 Assessor's Discussion - Safety

For the safety analysis to support frequencies of AR in the SmPC, a total of 180 individuals from the MYR 301 and MYR 203 (thereof 150 individuals from the MYR301 study) were included with the following distribution: 51 individuals in the delayed treatment arm, 64 individuals in the 2 mg BLV treatment arm and 65 individuals in the 10 mg BLV treatment arm.

In the MYR301 safety data set, 49% in the 2 mg BLV treatment group and 72% in the 10 mg BLV group experienced TEAEs related to the study drug. Only isolated SAEs were reported, and none of them evaluated as related to treatment.

TEAEs overrepresented in the BLV treatment groups compared to the delayed treatment arm, and at least probably causally related, are overall well reflected in the SmPC and comprise eosinophilia, pruritus, fatigue, injection site reactions, headache, arthralgia, nausea and total bile acid increased.

The MAH suggested updating the frequency of pruritus (currently common) and infection site reactions (currently common) to very common AEs in the SmPC, which is supported based on the presented data.

All common AEs that can be suspected to be causal to BLV treatment are reflected in the SmPC except asthenia and hypertension, which show a dose dependent increase in frequency. Nine cases of hypertension have been identified in the clinical trials for which the majority had risk factors or alternative explanations including pre-existing conditions. Three cases were identified post-marketing, all with plausible alternative explanations. It was agreed with the MAH that based on the totality of data there is insufficient evidence to support causality. The MAH suggestion to not include hypertension as an ADR in the SmPC section 4.8 was supported.

The MAH identified 9 cases of asthenia in the clinical trial program. In those cases, asthenia was in most of the cases mild to moderate and resolved in 5 cases. Patients had multiple underlying diagnoses ongoing such as concurrent infection (3), depression (2), lumbal sciatic pain (1) and hemiparesis which complicates the possibility to draw firm conclusion regarding causality with the drug. 16 post-marketing cases were identified, of which 14 cases presented alternative explanations including additional underlying diagnoses and comedication with Peg-INF (11 cases), for which asthenia is listed as a common event, which limits the possibility for a firm confirmation of causality. Although terms used to describe asthenia (e.g., "(episodic) weakness" or weak side of the body") or fatigue ("fatigue ", "tiredness " or "exhaustion") are not entirely interchangeably used, the aspect of a certain similarity is acknowledged. Thus, the suggestion of the MAH to not include as an additional separate term in section 4.8 was supported.

The benefit-risk remains positive.

9. Changes to the Product Information

As a result of this variation, sections 4.8 and 5.1 of the SmPC are being updated. The Package Leaflet (PL) is updated accordingly.

Changes are made to the Opinion Annex II conditions as detailed in the recommendations section above.

Editorial changes were also made to the PI.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.