HEPCLUDEX®

(Bulevirtide)

Authorization Number: 68338
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Clinical Study Results

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Gilead Sciences Switzerland Sàrl
General-Guisan-Strasse 8
6300 Zug
Switzerland

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1. INTRODUCTION

As of 2020, Gilead discloses clinical study results of newly authorized products in Switzerland by Swissmedic according to the requirements laid out in Art. 71-73 TPO (Ordinance on Therapeutic Products).

Below you will find the information for clinical studies relevant for the marketing authorization for Hepcludex® (Bulevirtide) in Switzerland.

2. OVERVIEW ON CLINICAL STUDIES

Study number	Study title:	Indication:	EudraCT-Number:
MYR 301	A Multicenter, Open-label, Randomized Phase 3 Clinical Study to Assess Efficacy and Safety of Bulevirtide in Patients with Chronic Hepatitis Delta	Chronic Hepatitis Delta	2019-001213-17

3. STUDY SYNOPSIS MYR301

STUDY SYNOPSIS

Study MYR301
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: A Multicenter, Open-label, Randomized Phase 3 Clinical Study to Assess Efficacy and Safety of Bulevirtide in Patients With Chronic Hepatitis Delta
Investigators: This is a multicenter study.
Study Centers: Participants were enrolled from a total of 16 study sites: 5 in Germany, 3 in Italy, 7 in Russia, 1 in Sweden.
Publications: Wedemeyer H, Aleman S, Andreone P, Blank A, Brunetto M, Bogomolov P, et al. Bulevirtide Monotherapy at Low and High Doses in Patients With Chronic Hepatitis Delta: 24 Weeks Interim Data of the Phase 3 MYR301 Study [Poster 2730]. European Association for the Study of the Liver (EASL): The Digital International Liver Congress; 2021 23-26 June. Wedemeyer H, Aleman S, Brunetto M, Blank A, Andreone P, Bogomolov P, et al. (2023) A Phase 3, Randomized Trial of Bulevirtide in Chronic Hepatitis D. N Engl J Med. 6;389(1):22-32. Wedemeyer H, Aleman S, Brunetto M, Andreone P, Blank A, Bogomolov P, et al. Efficacy and Safety at 96 Weeks of Bulevirtide 2 mg or 10 mg Monotherapy for Chronic Hepatitis D (CHD): Results from an Interim Analysis of a Phase 3 Randomized Study [Oral Presentation OS-068]. EASL The International Liver Congress; 2023 21-24 June; Vienna, Austria.
Study Period: 17 April 2019 (first participant screened) 26 November 2020 (last participant last visit for the primary endpoint and for the Week 48 report) 25 October 2021 (last participant last visit for this Week 96 report)
Phase of Development: Phase 3
Study Objectives and Endpoints: The objectives of this study were as follows:

Primary Objective	Primary Endpoint
• To evaluate the efficacy of bulevirtide (BLV [GS-4438], Hepcludex®) administered subcutaneously (SC) for 48 weeks at a dose of 2 mg or 10 mg once daily for treatment of chronic hepatitis delta infection (CHD) in comparison to delayed treatment	Primary Efficacy Endpoint • The proportion of participants achieving combined response at Week 48. Combined response was defined as fulfilment of 2 conditions simultaneously: — Undetectable (< lower limit of quantification [LLOQ], target not detected) hepatitis delta virus (HDV) RNA or decreased by ≥ 2 $\log_{10}$ IU/mL from baseline — Alanine aminotransferase (ALT) normalization
Secondary Objectives	**Secondary Endpoints and Additional Endpoints**
• To evaluate optimal treatment duration	Key Secondary Efficacy Endpoint • The proportion of participants with undetectable HDV RNA at Week 48 Other Secondary Efficacy Endpoints • The proportion of participants with ALT normalization at Week 48 • The proportion of participants with undetectable HDV RNA 24 weeks after scheduled end of treatment (sustained virologic response) • The proportion of participants with undetectable HDV RNA 48 weeks after scheduled end of treatment (sustained virologic response) • Change from baseline in liver stiffness as measured by elastography at Weeks 48, 96, 144, 192, and 240 Additional Efficacy Endpoint • The proportion of participants with HDV RNA decrease by ≥ 2 $\log_{10}$ IU/mL or undetectable HDV RNA at Week 48
• To assess the safety of BLV	Safety Endpoints • Frequency and nature of adverse events (AEs) (based on assessments of clinical events, physical examination, vital signs, electrocardiogram [ECG], and laboratory tests) • Changes in vital signs • Changes in RR, PQ, QRS, QT, QT interval corrected for heart rate (QTc; Bazett), and heart rate based on assessments of ECG • Changes in laboratory tests (hematology, coagulogram, biochemistry, blood bile salts, vitamin D)
Exploratory Objectives	**Exploratory Efficacy Endpoints**
(No associated exploratory objective for efficacy, with the exception of change in quality of life [QOL])	• The proportion of participants with a change from baseline in necroinflammation as assessed at liver biopsies (for available appropriate biopsy

	specimens) • The proportion of participants with a change from baseline in fibrosis as assessed at liver biopsies (for available appropriate biopsy specimens) • The proportion of participants with combined response at all postbaseline assessments of HDV RNA and ALT • The proportion of participants with HDV RNA decrease by ≥ 2 $\log_{10}$ IU/mL from baseline at all postbaseline assessments • The proportion of participants with undetectable HDV RNA at all postbaseline assessments • Change from baseline in HDV RNA at all postbaseline assessments • The proportion of participants with ALT normalization at all postbaseline assessments • Change from baseline in ALT at all postbaseline assessments • Change from baseline in serum alpha-2-macroglobulin (fibrosis marker) at all postbaseline assessments • The proportion of participants with hepatitis B surface antigen (HBsAg) response (HBsAg decrease by ≥ 1 $\log_{10}$ IU/mL) at all postbaseline assessments • The proportion of participants with HBsAg loss without seroconversion at all postbaseline assessments • The proportion of participants with HBsAg loss with seroconversion (presence of anti-HBsAg) at all postbaseline assessments • Change from baseline in HBsAg at all postbaseline assessments • Change from baseline in hepatitis B virus (HBV) DNA at all postbaseline assessments • Incidence of liver-related clinical events at all postbaseline assessments[a] • Number of liver-related hospitalizations and duration of each hospitalization at all postbaseline assessments • Appearance and concentration of anti-BLV antibodies • Resistance testing (HBV genotypic assay [sequencing analysis] with focus on the HBV envelope, phenotypic resistance assay and HDV genotypic assay [sequencing analysis]); sodium taurocholate cotransporting polypeptide (NTCP) polymorphism

	• Other parameters in liver biopsy samples (may include but not limited to quantitative analysis of HDV RNA, HBV DNA, HBV RNA, interferon stimulated genes, NTCP; semiquantitative analysis of HBsAg and hepatitis delta antigen with immunohistochemistry) • Hepatitis B e antigen (HBeAg) and hepatitis B e antibody (HBeAb) status at all postbaseline assessments (for participants with positive HBeAg at screening)
• To investigate influence of BLV on QOL	• Change from baseline in QOL assessed with questionnaires at all postbaseline assessments: — EuroQol (5 dimensions [EQ-5D-3L]) — Fatigue Severity Scale (FSS) — The Hepatitis Quality of Life Questionnaire™ (HQLQ™)
	Pharmacokinetic Endpoint
	• Plasma concentrations of BLV (by sparse pharmacokinetic[s] [PK] sampling)

a Liver-related clinical events: including but not limited to: cirrhosis development; liver decompensation including development or worsening jaundice, coagulopathy, ascites, hepatic encephalopathy, bleeding from varices and liver failure; hepatocellular carcinoma development; liver transplantation and liver-related death.

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

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

Delayed Treatment Group: 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

BLV 2-mg Treatment Group: Immediate treatment with BLV 2 mg/day for 144 weeks with a further follow-up period of 96 weeks

BLV 10-mg Treatment Group: 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).

This interim clinical study report describes study results when all participants had completed the Week 96 visit or had discontinued from the study.

Number of [Participants/Patients] (Planned and Analyzed):
Planned: 150
Analyzed: 150

Diagnosis and Main Criteria for Inclusion: Adult male and female participants, aged 18 to 65 years with CHD (≥ 6 months prior to screening) and positive polymerase chain reaction

results for serum/plasma HDV RNA, with or without liver cirrhosis, who had elevated ALT (> 1 × upper limit of normal [ULN], but < 10 × ULN), Child-Pugh score of ≤ 7 points, serum albumin > 28 g/L, creatinine clearance ≥ 60 mL/min (Cockcroft-Gault formula), total bilirubin < 34.2 µmol/L at screening. Participants with current or previous (within the past 2 years) decompensated liver disease were excluded. Participants with controlled human immunodeficiency virus coinfection were allowed.

Duration of Treatment: In the delayed treatment group, participants are treated for 96 weeks after starting treatment at Week 48. For the BLV 2-mg and BLV 10-mg treatment groups, treatment duration is 144 weeks. For all treatment groups there is a 96-week period of off-treatment follow-up (ie, a total of 240 weeks).

Test Product, Dose, Mode of Administration, and Batch No.:

Bulevirtide vials contain 2 or 5 mg lyophilized powder for injections. Bulevirtide 2 or 10 mg daily (10 mg from 2 × 5 mg vials) was administered subcutaneously and was supplied in sterile vials for reconstitution in 1 mL sterile water for injection prior to administration.

The table below presents a summary of the batch numbers and expiration dates for the investigational product evaluated in this study.

Strength	BLV 2 mg	BLV 5 mg
Batch No.	M218431 M218432 M219041 B219191 B219192 B219201 B219491 B219491G B220311 B221161	M518441 M518442 M519041 B519201 B519401 B519501D B519501 B520391 B521091D B521091
Expiration Date	April 2020 April 2020 July 2020 May 2021 May 2021 May 2021 December 2021 December 2021 July 2022 March 2023	May 2020 May 2020 July 2020 November 2020 January 2021 May 2021 December 2021 September 2022 February 2023 March 2023
Manufacturer/Supplier	LYOCONTRACT GmbH Pulverwiese 1 38871 Ilsenburg Germany	LYOCONTRACT GmbH Pulverwiese 1 38871 Ilsenburg Germany

Site of Release in Europe	Nuvisan GmbH Wegenerstrasse 13 89231 Neu-Ulm Germany and LYOCONTRACT GmbH Pulverwiese 1 38871 Ilsenburg Germany	Nuvisan GmbH Wegenerstrasse 13 89231 Neu-Ulm Germany and LYOCONTRACT GmbH Pulverwiese 1 38871 Ilsenburg Germany

Reference Therapy, Dose, Mode of Administration, and Batch No.:

None.

Statistical Methods:

Efficacy:

Primary Efficacy Endpoint

The primary efficacy endpoint was the combined response at Week 48 defined as fulfilling both of the following criteria: 1) undetectable HDV RNA (HDV RNA < LLOQ, target not detected) or decrease in HDV RNA by ≥ 2 $\log_{10}$ IU/mL from baseline, and 2) ALT normalization. Two 2-sided Fisher's exact tests at an overall significance level of 0.05 were performed to sequentially test the hypotheses:

H_{01}: $p_O = p_{M\ 10\ mg}$ versus H_{11}: $p_O \neq p_{M\ 10mg}$

H_{02}: $p_O = p_{M\ 2\ mg}$ versus H_{12}: $p_O \neq p_{M\ 2mg}$

where p_O, $p_{M\ 2mg,}$ and $p_{M\ 10mg}$ are the expected response rate for delayed treatment, BLV 2 mg and BLV 10 mg, respectively. In terms of a hierarchical testing procedure, the second null hypothesis was not to be rejected if the first null hypothesis could not be rejected. These hypotheses were tested at the planned Week 24 interim analysis and at the Week 48 primary analysis. To account for the repeated analysis, the nominal two-sided significance level of 0.05 were split among these 2 time points with 0.01 for Week 24 interim analysis and 0.04 for Week 48 primary analysis.

The primary analysis of combined response at Week 24 is the estimated rate difference between the BLV treatment groups and the delayed treatment group with 99% exact unconditional CIs for the difference based on the score statistic. The *P* value from 2 two-sided Fisher's exact tests were also provided. There was a statistically significant difference at Week 24 if $P < 0.01$. The comparison of BLV 2 mg versus delayed treatment was considered significant only if the comparison of BLV 10 mg versus delayed treatment was significant. In addition, for each treatment group, the response rate with Clopper-Pearson 95% CIs were presented.

The primary analysis of combined response at Week 48 is the estimated rate difference between the BLV treatment groups and the delayed treatment group with 96% exact unconditional CIs for the difference based on the score statistic. The *P* value from 2 two-sided Fisher's exact tests was also provided. 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 BLV 10 mg versus delayed treatment was significant. In addition, for each treatment group, the response rate with Clopper-Pearson 95% CIs was presented.

The primary efficacy analysis was conducted when all participants completed the Week 48 visit or discontinued from the study prematurely (before Week 48), based on the Full Analysis Set (FAS). The primary efficacy endpoint was also examined using the Per Protocol (PP) Analysis Set and using the subgroup presence or absence of cirrhosis at randomization. The sensitivity analysis for primary endpoint was the same analysis as primary analysis by using the data for which missing values were imputed as failure regardless of whether it was related to COVID-19.

For analyses of the primary endpoint at Week 24 and Week 48 using FAS, missing imputed as nonresponse (missing equals failure [M = F]) was adopted when missing was not related to COVID-19. Missing value was imputed using the last observation (including observation from unscheduled visit) when missing was related to COVID-19 (except the sensitivity analysis in which all missing value imputed as failure).

Secondary Efficacy Endpoint

The proportion of participants with undetectable HDV RNA at Week 48 is the key secondary endpoint and was used to test differences between the 2 BLV doses and hence evaluate the dose response relationship.

A two-sided Fisher's exact test was performed to test the hypotheses

H_{03}: $r_{M2mg} = r_{M\ 10mg}$ versus H_{13}: $r_{M2mg} \neq r_{M\ 10mg}$

where $r_{M\ 2mg}$, $r_{M\ 10mg}$ are the expected rates of participants with undetectable HDV RNA at Week 48 for BLV 2 mg and BLV 10 mg, respectively.

This test was performed as the 2 null hypotheses for the primary variable (H_{01} and H_{02}) both were rejected. As for the primary analysis, the above hypotheses were tested at the interim analysis at Week 24 and hence the nominal 2-sided significance level of 0.05 was split among the time points with 0.01 for Week 24 and 0.04 for Week 48. The estimated rate differences between BLV 10 mg and BLV 2 mg with exact unconditional CI based on score statistic (99% CI for Week 24 and 96% CI for Week 48), and the *P* value from Fisher's exact test were provided using FAS and PP Analysis Set. The Clopper-Pearson 95% CIs of undetectable HDV RNA rate in each treatment group was presented. The same summary was repeated by presence or absence of cirrhosis. For analyses of undetectable HDV RNA at Week 24 and Week 48 using FAS, M = F was adopted when missing was not related to COVID-19. Missing value was imputed using the last observation (including observation from unscheduled visit) when missing was related to COVID-19.

The proportion of participants with ALT normalization at Week 48 was compared between the BLV 2-mg treatment group and the delayed treatment group and the BLV 10-mg treatment group and the delayed treatment group using 2-sided Fisher's exact tests. Nominal *P* values without multiple comparison adjustment and 95% exact unconditional CIs based on score statistic for the proportion differences were provided. The same analysis is performed at Week 24 and at Week 48, using FAS and using PP Analysis Set. In addition, for each treatment

group, the Clopper-Pearson 95% CIs of response rate will also be presented. The same summaries were repeated by presence or absence of cirrhosis.

For the change from baseline in liver stiffness at Week 48, an analysis of covariance (ANCOVA) model was used to compare the least squares (LS) means between the BLV 2-mg treatment group and the delayed treatment group, and the BLV 10-mg treatment group and the delayed treatment group, using FAS and PP Analysis Set. The model included treatment, region, presence of cirrhosis, and baseline liver stiffness as covariates. Nominal *P* values without multiple comparison adjustment and the 95% CI for the LS mean difference between each BLV treatment group and the delayed treatment group were provided. In addition, for each treatment group, the LS mean was provided.

For the change from baseline in liver stiffness at Week 96, a mixed-effects model for repeated measures (MMRM) was used to evaluate treatment effect using FAS. The model includes treatment group, region, presence of cirrhosis, visit and treatment-by-visit interaction as fixed effects, and baseline liver stiffness as covariable. An unstructured variance-covariance matrix was used. The Kenward-Roger method was used to estimate the degrees of freedom. Restricted maximum likelihoods was used to fit the model. Missing change values was not otherwise imputed using MMRM. For each treatment group, the LS mean with 95% CI at Week 96 were presented. In addition, the difference in LS means and the 95% CI for the LS mean difference between each BLV treatment group and delayed treatment were provided.

Descriptive statistics of liver stiffness at each visit, as well as the change from baseline, was provided by treatment group. The summary was repeated by presence or absence of cirrhosis.

For all binary response endpoints using FAS (except primary efficacy endpoint of combined response and key secondary efficacy endpoint of undetectable HDV RNA at Week 24 and Week 8), missing values were imputed as nonresponder.

No separate PP Analysis Set was defined for the interim Week 96 analysis. Hence, no efficacy analyses using the PP Analysis Set were performed for the interim Week 96 analysis. The Week 48 primary analysis were repeated for primary efficacy endpoint of combined response, the key secondary endpoint of undetectable HDV RNA, and the secondary endpoint of ALT normalization using the updated Week 96 database to ensure the ongoing collection and data cleaning after the Week 48 primary analysis would not have an impact on the combined response generated at Week 48, as well as undetectable HDV RNA at Week 48, and ALT normalization at Week 48, using FAS and PP Analysis Set determined at Week 48.

Pharmacokinetics:

Descriptive statistics (sample size, number of participants with evaluable/missing mean, SD, percentage coefficient of variation [%CV], minimum, median interquartile range, maximum, first quartile [Q1], third quartile [Q3], geometric mean, and its 95% CI) were presented by visit for plasma concentration data.

Safety:

The AE, clinical laboratory, body weight, vital signs, prior and concomitant medication, and ECG data were summarized using descriptive statistics.

Adverse events were coded using MedDRA, Version 24.1. Safety data were summarized by treatment group using the Safety Analysis Set, which included participants randomized to the delayed treatment group or randomized to BLV treatment groups and received BLV at least once after randomization.

Adverse events were presented by primary system organ class and preferred term (PT). The analysis focused on the treatment-emergent adverse events (TEAEs).

For Week 96 interim analysis, a TEAE was defined as the following:

- For the BLV 2-mg and BLV 10-mg treatment groups, the TEAEs are defined as one or both of the following:
  - Any AEs with an onset date on or after the study drug start date and no later than 30 days after permanent discontinuation of study drug
  - Any AEs leading to premature discontinuation of study drug (BLV)
- For the delayed treatment group, TEAEs are defined as one of the following:
  - Any AEs with an onset date on or after the randomization date and no later than 30 days after permanent discontinuation of study drug if the participant switched to BLV after Week 48 visit
  - Any AEs leading to premature discontinuation of study drug BLV
  - Any AEs with an onset date on or after the randomization date and no later than the study discontinuation date, if participants discontinued study before switching to BLV at Week 48 visit

The frequency of TEAEs was summarized by participant incidences. In these summaries, each participant was counted only once within each PT.

Frequencies of TEAEs are also presented by relationship to study treatment and by maximum severity. Additional analyses were performed for serious adverse events (SAEs), regardless of whether or not the events were treatment emergent (TE); TE SAEs; and AEs leading to discontinuation.

Vital signs and laboratory parameters were described by summary statistics for measured values and changes from baseline by visit.

Descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) were provided by treatment group for each clinical laboratory analyte in tables with baseline values, values and change from baseline at each postbaseline visit up to Week 96. Additionally, shifts in assessments from baseline value (low, normal, and high) to each visit up to Week 96 were presented (shift tables).

Physical examination findings were summarized or provided in listings.

The number and percentages of participants with normal/abnormal not clinically significant/abnormal clinically significant findings in physical examinations were presented by visit and treatment group, as were the number and percentages of participants with production of BLV antibodies.

SUMMARY OF RESULTS:

Participant Disposition and Demographics:

A total of 183 participants were screened for this study, and 33 participants failed screening and 150 were randomized (delayed treatment [DT] group: 51 participants; BLV 2-mg treatment group: 49 participants; BLV 10-mg treatment group: 50 participants). At baseline, 99 participants had received at least 1 dose of study drug (BLV 2-mg treatment group: 49 participants; BLV 10-mg treatment group: 50 participants). At Week 48, among the 51 participants who were randomized to the DT group, 50 participants received study drug (BLV 10 mg) starting at the Week 48 visit (DT to BLV 10-mg group for analysis after Week 48). Unless specified otherwise, the original 51 participants were included in DT group for analysis before Week 48, and the 50 participants receiving BLV at Week 48 were included in the DT to BLV 10-mg group for analysis after Week 48, with a baseline reset at Week 48 for applicable endpoints. Overall, by Week 96, 149 participants were treated with BLV (DT to BLV 10-mg group: 50 participants; BLV 2-mg treatment group: 49 participants; BLV 10-mg treatment group: 50 participants) at 16 sites in 4 countries: 85 in Russia, 26 in Germany, 24 in Italy, and 14 in Sweden. Four participants failed screening at 1 site in the United States.

Of the 150 randomized participants, 7 participants discontinued the study prior to the Week 96 data cutoff date. The reasons for discontinuation were withdrawal of consent (BLV 2-mg treatment group: 2 participants; BLV 10-mg treatment group: 2 participants), pregnancy (DT group before receiving treatment with BLV 10 mg: 1 participant), death (DT group following treatment with BLV 10 mg: 1 participant), and physician's decision (BLV 10-mg treatment group: 1 participant).

The median age was 41.0 years (range: 19 to 62 years). Overall, the majority of participants were White (82.7%), and over half of the participants were male (57.3%). The overall median (Q1, Q3) value for body mass index at baseline was 24.76 (22.40, 27.04) kg/m^2.

Baseline disease characteristics were generally similar among the 3 treatment groups assessed at original baseline (at randomization). In addition, baseline disease characteristics for the subjects randomized to DT group remained similar at Week 48 when they were initiated with BLV compared with the original baseline at randomization, with some exceptions; notably, mean (SD) serum ALT was 101.6 (61.9) U/L at original baseline (at randomization) and 82 (51.1) U/L at Week 48.

Efficacy Results:

Both doses of BLV demonstrated superiority over delayed treatment at Week 48 in efficacy variables (combined response, virologic and biochemical responses, and liver stiffness improvements). In addition, efficacy continuously improved over time for participants receiving BLV 2 mg and 10 mg through 96 weeks of treatment. In subgroups of participants with and without cirrhosis, there was a consistent treatment effect for both BLV doses.

The Week 96 results for participants in the DT group (representing 48 weeks of treatment with BLV 10 mg) were generally comparable to the Week 48 results for participants randomized to immediate BLV 10 mg treatment.

Primary Efficacy Endpoint

Combined Response at Week 48

At Week 48, a significantly greater proportion of participants in both the BLV 2-mg and BLV 10-mg treatment groups achieved the primary efficacy endpoint (combined response) compared with the control group (delayed treatment). The proportion of participants who achieved combined response in the active treatment groups was as follows:

- BLV 2-mg treatment group: 44.9% (95% CI: 30.7%-59.8%); $P < 0.0001$ when compared with the DT group (2.0% [95% CI: 0.0%-10.4%])
- BLV 10-mg treatment group: 48.0% (95% CI: 33.7%-62.6%); $P < 0.0001$ when compared with the DT group (2.0% [95% CI: 0.0%-10.4%])

The differences in proportions (96% CI) of responders at Week 48 for the combined response between each of the BLV treatment groups and the DT group were as follows; the differences were statistically significant for both BLV treatment groups:

- BLV 2-mg treatment group versus the DT group: 42.9% (96% CI: 27.0%-58.5%; $P < 0.0001$)
- BLV 10-mg treatment group versus the DT group: 46.0% (96% CI: 30.5%-61.4%; $P < 0.0001$)

Secondary Efficacy Endpoints

Undetectable HDV RNA at Week 48 (Key Secondary Efficacy Endpoint)

The proportion of responders for undetectable HDV RNA for the BLV 2-mg treatment group was 12.2% and for the BLV 10-mg treatment group was 20.0%, and the difference between the BLV 2-mg and BLV 10-mg treatment groups was not statistically significant ($P = 0.4139$).

ALT Normalization at Week 48

Similar proportions of participants in the BLV 2-mg and BLV 10-mg treatment groups achieved a normalized ALT response at Week 48:

- BLV 2-mg treatment group: 51.0% (95% CI: 36.3%-65.6%); $P < 0.0001$ when compared with the DT group (11.8% [95% CI: 4.4%-23.9%])
- BLV 10-mg treatment group: 56.0% (95% CI: 41.3%-70.0%); $P < 0.0001$ when compared with the DT group (11.8% [95% CI: 4.4%-23.9%])

Change From Baseline in Liver Stiffness at Week 48 and Week 96

At Week 48, there was a mean decrease in liver stiffness for both BLV treatment groups, and the difference in LS means, when compared with the DT group, was statistically significant. Liver stiffness consistently decreased with prolonged BLV treatment duration. The LS means (95% CI) at Week 48 and Week 96 for change from baseline in liver stiffness were as follows:

- Week 48
  - BLV 2-mg treatment group: −3.08 kPa (−4.70 to −1.46); $P = 0.0010$ when compared with the DT group (0.88 kPa [95% CI: −0.80% to 2.56%])

— BLV 10-mg treatment group: −3.17 kPa (95% CI: −4.90% to −1.44%); $P = 0.0010$ when compared with the DT group (0.88 kPa [95% CI: −0.80%-2.56%])

- Week 96
  - — BLV 2-mg treatment group: −4.0 kPa (95% CI: −5.6% to −2.5%)
  - — BLV 10-mg treatment group: −4.7 kPa (95% CI: −6.3% to −3.2%)
  - — DT group (with baseline at randomization, N = 51): −3.0 kPa (95% CI: −4.6 to −1.5%)

Additional Efficacy Endpoint

HDV RNA Decrease by ≥ 2 log_{10} IU/mL From Baseline or Undetectable HDV RNA at Week 48 (Virologic Response)

The proportions of participants achieving virologic response at Week 48 in the BLV treatment groups were as follows:

- BLV 2-mg treatment group: 73.5% (95% CI: 58.9%-85.1%); $P < 0.0001$ when compared with the DT group (3.9% [95% CI: 0.5%-13.5%])
- BLV 10-mg treatment group: 76.0% (95% CI: 61.8%-86.9%); $P < 0.0001$ when compared with the DT group (3.9% [95% CI: 0.5%-13.5%])

Exploratory Efficacy Endpoints

Combined Response Over Time

Combined response continuously improved over time for participants receiving BLV 2 mg and 10 mg through 96 weeks of treatment and was similar between the BLV 2-mg and 10-mg treatment groups as presented below:

- BLV 2-mg treatment group:
  - — Week 24: 34.7%
  - — Week 48: 44.9%
  - — Week 96: 55.1%
- BLV 10-mg treatment group:
  - — Week 24: 28.0%
  - — Week 48: 48.0%
  - — Week 96: 56.0%

At Week 48 (before BLV treatment had commenced), the proportion of responders in the DT group was 2.0%. At Week 96, the proportion of responders in the DT to BLV 10-mg group was 42.0% (with baseline reset at Week 48, N = 50), which is comparable to the response rate at Week 48 for the immediate BLV 10-mg treatment group (48.0%).

HDV RNA Decrease by ≥ 2 log10 IU/mL From Baseline or Undetectable HDV RNA (Virologic Response) Over Time

Virologic response rate continuously improved over time for participants receiving BLV 2 mg and 10 mg through 96 weeks of treatment. The virologic response rate in the BLV 10-mg treatment group was either similar or numerically higher than the BLV 2-mg treatment group as presented below.

- BLV 2-mg treatment group:
  - Week 24: 55.1% (95% CI: 40.2%-69.3%)
  - Week 48: 73.5% (95% CI: 58.9%-85.1%)
  - Week 96: 75.5% (95% CI: 61.1%-86.7%)
- BLV 10-mg treatment group:
  - Week 24: 66.0% (95% CI: 51.2%-78.8%)
  - Week 48: 76.0% (95% CI: 61.8%-86.9%)
  - Week 96: 82.0% (95% CI: 68.6%-91.4%)

In the DT group, at Week 48 (before BLV treatment was commenced), the proportion of participants achieving virologic response was 3.9%. At Week 96, in the DT to BLV 10-mg group (with baseline reset at Week 48, N = 50), the proportion of participants achieving virologic response was 96%.

Undetectable HDV RNA Over Time

Undetectable HDV RNA response rates continuously improved over time for participants receiving BLV 2 mg and 10 mg through 96 weeks of treatment and were numerically higher in the BLV 10-mg treatment group, as presented below.

- BLV 2-mg treatment group:
  - Week 24: 6.1% (95% CI: 1.3%-16.9%)
  - Week 48: 12.2% (95% CI: 4.6%-24.8%)
  - Week 96: 20.4% (95% CI: 10.2%-34.3%)
- BLV 10-mg treatment group:
  - Week 24: 8.0% (95% CI: 2.2%-19.2%)
  - Week 48: 20.0% (95% CI: 10.0%-33.7%)
  - Week 96: 36.0% (95% CI: 22.9%-50.8%)

In the DT group, at Week 48 (before BLV treatment was commenced), no participants had undetectable HDV RNA. At Week 96, in the DT to BLV 10-mg group (with baseline reset at Week 48, N = 50), the proportion of participants with undetectable HDV RNA was 24.0%.

ALT Normalization Over Time

ALT normalization response rates continuously improved over time for participants receiving BLV 2 mg and 10 mg through 96 weeks of treatment and were similar between both BLV doses.

- BLV 2-mg treatment group:
  - Week 24: 53.1% (95% CI: 38.3%-67.5%)
  - Week 48: 51.0% (95% CI: 36.3%-65.6%)
  - Week 96: 63.3% (95% CI: 48.3%-76.6%)
- BLV 10-mg treatment group:
  - Week 24: 38.0% (95% CI: 24.7%-52.8%)
  - Week 48: 56.0% (95% CI: 41.3%-70.0%)
  - Week 96: 64.0% (95% CI: 49.2%-77.1%)

In the DT group, at Week 48 (before BLV treatment was commenced), the proportion of participants with normalized ALT was 11.8%. At Week 96, in the DT to BLV 10-mg group (with baseline reset at Week 48, N = 50), the proportion of participants with normalized ALT was 44.0%.

Fibrosis and Necroinflammation

Improvements in fibrosis and necroinflammation (histological activity stage) parameters were seen in the BLV treatment groups compared with the DT group at Week 48.

HBsAg Response

No participant across the treatment groups experienced HBsAg loss with or without seroconversion through Week 96. Small mean changes from baseline in serum HBsAg levels were observed across the 3 treatment groups over 96 weeks.

HBV DNA Response

At baseline, mean (SD) HBV DNA levels were low in all treatment groups. At Week 48, the LS means change in HBV DNA levels was small in both BLV treatment groups. The difference in LS means between the BLV treatment groups and the DT group was statistically significant for the BLV 10-mg treatment group only ($P = 0.2018$ for the BLV 2-mg treatment group and $P = 0.0095$ for the BLV 10-mg treatment group). The mean (SD) changes from baseline in HBV DNA levels at Weeks 48 and 96 were numerically greater in the BLV 10-mg treatment group.

- BLV 2-mg treatment group:
  - Week 48: −0.490 (0.989) IU/mL
  - Week 96: −0.583 (1.305) IU/mL
- BLV 10-mg treatment group:
  - Week 48: −0.667 (1.202) IU/mL
  - Week 96: −0.599 (1.073) IU/mL
- DT group (with baseline at randomization, N = 51):
  - Week 48: −0.091 (0.926) IU/mL

— Week 96: −0.363 (0.889) IU/mL

HBeAg Loss Over Time

In the small subset of participants who were HBeAg positive at baseline, none experienced loss by Week 96.

Liver-Related Clinical Events

From baseline through Week 96 there was only 1 liver-related clinical event (development of ascites) that occurred in a participant in the DT group who had cirrhosis, after switching to BLV 10 mg treatment, between Week 48 and 96. There were no liver-related hospitalizations.

Quality of Life Questionnaires

Week 48

At Week 48, scores for the individual EQ-5D-3L domains, EuroQol visual analogue scale (EQ-VAS), FSS, and HQLQ components were generally similar between each of the BLV treatment groups when compared with the DT group, with the exception of the EQ-VAS and some components of the HQLQ, in which there was a significant improvement in the BLV treatment groups compared with the DT group. However, the significant improvement was generally not observed consistently across the 2 BLV treatment groups. These results should be interpreted with caution, as multiple endpoints were tested and the study was not powered to test these exploratory endpoints.

Week 96

At Week 96, the results for quality of life questionnaires were consistent with the Week 48 results.

Pharmacokinetics Results:

Descriptive analysis of the plasma concentrations up to Week 96 demonstrated that BLV reaches steady state by Week 4, beyond which a consistent PK is observed in all BLV dose groups. As expected, the concentrations were higher in the BLV 10-mg treatment group than in the BLV 2-mg treatment group. High variability in BLV plasma concentrations was observed in all BLV dose groups, with %CV ranging from 66.8% to 152% across time points. In addition, the geometric mean BLV concentration observed at Week 96 for the DT group, representing 48 weeks of treatment with BLV 10 mg, was similar to that observed with the BLV 10 mg at Week 48.

Safety Results:

Study treatment with BLV at 2 mg and 10 mg doses once daily was generally safe and well tolerated through a mean (SD) duration of exposure to study drug of 94.44 (8.22) weeks and 91.10 (20.32) weeks in the BLV 2-mg and BLV 10-mg treatment groups, respectively. The mean (SD) duration of exposure to study drug between Weeks 48 and 96 for the DT to BLV 10 mg group was 47.53 (4.24) weeks.

Adverse Events

Higher proportions of participants experienced TEAEs in both immediate BLV treatment groups by Week 96 compared with Week 48, likely due to the increased duration of study drug exposure (Week 48: BLV 2 mg:83.7%, BLV 10 mg: 88.0%; Week 96: BLV 2 mg: 95.9%, BLV 10 mg: 96.0%).

Through Week 48, the most frequently reported AEs by treatment group were as follows:

- DT group (no BLV treatment): leukopenia (17.6%, 9 participants); vitamin D deficiency (15.7%, 8 participants); and thrombocytopenia (13.7%, 7 participants)
- BLV 2-mg treatment group: headache (18.4%, 9 participants); leukopenia (14.3%, 7 participants each); 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); pruritus (16.0%, 8 participants); fatigue (14.0%, 7 participants); vitamin D deficiency (12.0%, 6 participants); and leukopenia, thrombocytopenia, eosinophilia, neutropenia, abdominal pain upper, and injection site erythema (10.0%, 5 participants each)

By Week 96, the most frequently reported AEs by treatment group were as follows:

- DT to BLV 10-mg group (Weeks 48-96): vitamin D deficiency (20.0%, 10 participants); headache and thrombocytopenia (14.0%, 7 participants each); and leukopenia (10.0%, 5 participants)
- BLV 2-mg treatment group: vitamin D deficiency (30.6%, 15 participants); headache and leukopenia (18.4%, 9 participants each), thrombocytopenia, fatigue, and lymphopenia (14.3%, 7 participants each); neutropenia, pruritus, and arthralgia (12.2%, 6 participants each); and eosinophilia (10.2%, 5 participants)
- BLV 10-mg treatment group: vitamin D deficiency (34.0%, 17 participants); headache (24.0%, 12 participants); fatigue and pruritus (18.0%, 9 participants); neutropenia (16.0%, 8 participants); leukopenia and thrombocytopenia (14.0%, 7 participants); lymphopenia and nausea (12.0%, 6 participants); and eosinophilia, arthralgia, injection site erythema, injection site reaction, and abdominal pain upper (10.0%, 5 participants)

Few participants had SAEs and no SAEs were considered related to study drug.

No participant discontinued study drug due to an AE and 1 death was reported in the DT group, which was not considered treatment related.

Hepatic Safety

A targeted group of MedDRA PTs was used to search for cases of hepatic AEs potentially indicative of hepatic flare. Up to Week 96, all hepatic AEs were Grade 1 or 2 in severity, and none resulted in discontinuation of study drug. Most hepatic laboratory abnormalities were Grade 1 or 2; there were 2 participants who had Grade 3 or 4 hepatic laboratory abnormalities.

An analysis of potential drug-induced liver toxicity was performed using the following 3 laboratory-based criteria: ALT and/or aspartate aminotransferase (AST) > 3 × ULN and total bilirubin > 2 × ULN; ALT > 5 × ULN; and total bilirubin > 2 × ULN.

Participants who met the criteria only at baseline were excluded from the analyses. There were 19.6% (10 of 51) of participants in the DT group who met the specified criteria up to Week 48 (without BLV treatment) and 2.0% (1 of 50) of participants in the DT group between Weeks 48 and 96 while receiving treatment with BLV 10 mg. In the immediate BLV treatment groups by Week 96, 16.2% (16 of 99) of participants met the specified criteria while on treatment: 10 participants in the BLV 2-mg treatment group and 6 participants in the BLV 10-mg treatment group. None of these events were considered Hy's Law cases due to potential alternative etiologies from underlying HDV infection and medical history.

Renal Safety

As bile salts are renally excreted and elevation of bile salts often occur during treatment with BLV, renal safety with BLV treatment was evaluated.

Through Week 96, the incidences of AEs of renal and urinary disorders were low across all treatment groups. When comparing participants with normal renal function (creatinine clearance ≥ 90 mL/min) and mild renal insufficiency (≥ 60 to < 90 mL/min), slightly higher bile salts levels were observed in participants with normal renal function at the BLV 2-mg dose. However, at the BLV 10-mg dose, bile salt elevations appeared marginally increased in participants with mild renal impairment compared to those with normal renal function, although the number of participants with mild renal impairment in the BLV 10-mg treatment group was small (n = 10). In addition, the safety profile was similar between participants with normal function and mild renal insufficiency across treatment groups.

Eosinophilia

Eosinophilia was assessed by reported AEs and by laboratory data analyzed for participants with persistently elevated eosinophils. At Week 48, the proportion of participants with AEs of eosinophilia was10.2% (5 participants) in the BLV 2-mg treatment group and 10.0% (5 participants) in the BLV 10-mg treatment group. One participant (2.0%) in the BLV 10 mg treatment group and 1 participant (2.0%) in the DT group experienced an AE of eosinophil count increased.

By Week 96, the proportion of participants with AEs of eosinophilia and eosinophil count increased in the immediate BLV treatment groups did not change from the profile at Week 48. One participant (2.0%) in the DT to BLV 10-mg group experienced an AE of eosinophilia between Weeks 48 and 96.

Injection Site Reactions

As BLV was administered by SC injection, injection site reactions were evaluated and all AEs with high-level term (HLT) "injection site reactions" were included in the analysis.

Adverse events from the HLT "injection site reactions" occurred in the immediate BLV treatment groups, with higher rates in the BLV 10-mg treatment group (30.0% at Weeks 48 and 96) than in the BLV 2-mg treatment group (18.4% and 20.4% at Weeks 48 and 96, respectively). 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 injection site reaction AEs were Grade 1 or 2 in severity, and none resulted in discontinuation of study drug.

In addition, local reactions at the injection site were evaluated by the investigator according to the tables for clinical abnormalities from "Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials." All but 2 of the observed local reactions at injection sites were of mild severity (1 participant in the BLV 2-mg treatment group with moderate pain and 1 participant in the BLV 10 mg treatment group with moderate erythema/redness).

Hypersensitivity, Angioedema, and Anaphylactic/Anaphylactoid Responses

No participants experienced an anaphylactic reaction or anaphylactoid response. One participant in the BLV 2-mg treatment group experienced an AE of angioedema that was nonserious, Grade 2 in severity, and not considered related to BLV therapy.

Skin and Subcutaneous Disorders

Skin and subcutaneous disorder AEs were experienced by a similar percentage of participants at Weeks 48 and 96 in the BLV 2-mg treatment group (18.4%, 9 participants and 20.4%, 10 participants, respectively) and the BLV 10-mg treatment group (26.0%, 13 participants and 28.0%, 14 participants, respectively). The proportion of participants experiencing skin and subcutaneous disorders AEs in the DT to BLV 10-mg group between Weeks 48 and 96 (N = 50) was 4.0% (2 participants). All skin and subcutaneous disorder AEs were Grade 1 or 2 in severity, and none resulted in discontinuation of study drug.

Increased Bile Salts

Bile salt elevations are mechanistically related to the binding of the NTCP receptor by BLV. Per the 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 over 96 weeks. The incidence of total bile salts increased AEs was low for both BLV treatment groups (BLV 2-mg treatment group: 2.0%, 1 participant; BLV 10-mg treatment group: 4.0%, 2 participants) through Week 96. One of 51 participants (2.0%) in the DT group had a treatment-related AE of total bile salts increased while receiving treatment with BLV 10 mg, between Weeks 48 and 96.

Bile salts have been reported in the literature to be associated with skin conditions. Due to the effect of BLV on increasing levels of bile salts, particular attention was paid to skin disorders including pruritus and other skin conditions, and the anaphylactic/anaphylactoid response. No participants experienced an anaphylactic reaction or anaphylactoid response, and while the bile salt levels in the BLV 10-mg treatment group were expectedly higher compared with the BLV 2-mg treatment group, there was no clear correlation between the presence of pruritus and the levels of bile salts in either the BLV 2-mg or immediate BLV 10-mg treatment group.

Through 96 weeks of treatment, dose-dependent elevations of bile salts were observed with BLV treatment and were asymptomatic and not related to any sequelae.

Graded Laboratory Abnormalities

Most participants had at least 1 laboratory abnormality by Week 48, the rates of which were similar across all treatment groups (delayed treatment group: 86.3%, 44 participants; BLV 2-mg treatment group: 89.8%, 44 participants; BLV 10-mg treatment group: 88.0%,

44 participants). A similar percentage of participants in each treatment group had Grade 3 or 4 laboratory abnormalities (DT group: 11.8%, 6 participants; BLV 2-mg treatment group: 12.2%, 6 participants; BLV 10-mg treatment group: 10.0%, 5 participants).

There was a similar trend for the Week 96 data: the majority of participants had at least 1 graded laboratory abnormality (DT group: 96.1%, 49 participants; BLV 2-mg treatment group: 93.9%, 46 participants; BLV 10-mg treatment group: 90.0%, 45 participants). For the majority of participants, the highest grade of reported abnormality was Grade 1 (DT group: 51.0%, 26 participants; BLV 2-mg treatment group: 44.9%, 22 participants; BLV 10-mg treatment group: 38.0%, 19 participants) or Grade 2 (DT group: 31.4%, 16 participants; BLV 2-mg treatment group: 30.6%, 15 participants; immediate BLV 10-mg treatment group: 34.0%, 17 participants).

Other Results:

Two participants, both of whom were in the BLV 10-mg treatment group, were antidrug antibody (ADA)-positive at baseline. Over the 48-week treatment period, 22.4% (11 of 49) of participants treated in the BLV 2-mg treatment group and 18.0% (9 of 50) of participants treated in the BLV 10-mg treatment group were ADA-positive, while the ADA-positive rates were 26.5% and 18.0% by Week 96, respectively, indicating that ADA prevalence was not impacted by dose, and longer treatment did not result in significantly higher ADA-positive rates.

In the DT group (N = 51), 5 participants (9.8%) were positive for ADA by Week 96 (representing 48 weeks of treatment with BLV 10 mg).

There was no impact of ADA presence on safety, as assessed by incidence of the most commonly-reported AEs in the ADA subgroups.

CONCLUSIONS:

The conclusions from this interim analysis of Study MYR301 are as follows:

- At Week 48, there was a statistically significant treatment effect for participants receiving BLV 2 mg or BLV 10 mg when compared with participants in the DT group.
  - For the primary efficacy endpoint of combined response at Week 48, 44.9% (95% CI: 30.7%-59.8%, $P < 0.0001$) and 48.0% (95% CI: 33.7%-62.6%, $P < 0.0001$) of participants achieved this endpoint in the BLV 2-mg and BLV 10-mg treatment groups, respectively, compared with 2.0% (95% CI: 0.0%-10.4%) of participants in the DT group.
  - For the key secondary efficacy endpoint of undetectable HDV RNA at Week 48, 12.2% (95% CI: 4.6%-24.8%) and 20.0% (95% CI: 10.0%-33.7%) of participants in the BLV 2-mg and 10-mg treatment groups achieved this endpoint, respectively, and the difference between BLV 2-mg and BLV 10-mg treatment groups was not statistically significant ($P = 0.4139$).
  - Higher rates of ALT normalization at Week 48 were seen in both of the BLV treatment groups compared with the DT group ($P < 0.0001$ for each BLV treatment group).

- — At Week 48, there were statistically significant mean decreases in liver stiffness for both BLV treatment groups that continuously decreased with longer BLV treatment duration through 96 weeks.
- — High proportions of participants in both BLV treatment groups achieved statistically significant virologic response (HDV RNA decrease by ≥ 2 $\log_{10}$ IU/mL from baseline or undetectable HDV RNA) at Week 48 compared with the DT group.

- With 96 weeks of continuous treatment, there was a continuously improved treatment effect over time for participants receiving BLV 2 mg and 10 mg, including combined response, virologic and biochemical responses, and liver stiffness improvements.
  - — Combined response rates increased progressively over 96 weeks of treatment and remained similar between both doses of BLV, with rates of 44.9% and 48.0% for the BLV 2-mg and 10-mg treatment groups at Week 48 and 55.1% and 56.0% for the BLV 2-mg and 10-mg treatment groups at Week 96.
  - — The Week 96 results for participants in the DT group (representing 48 weeks of treatment with BLV 10 mg) were generally comparable to the Week 48 results for participants randomized to receive immediate BLV 10 mg.
- Virologic and biochemical improvements were consistent in subgroups with and without cirrhosis for both doses of BLV.
- Bulevirtide was generally safe and well tolerated by participants with CHD. Common AEs were consistent with events expected in the participant population and with the known safety profile of the study drug.
- Safety was maintained over 96 weeks of BLV treatment, and both doses had a similar safety profile observed when BLV 10 mg treatment was delayed compared with the equivalent exposure at Week 48 for the immediate BLV 10-mg treatment group.
- Injection site reactions were very commonly observed in participants treated with BLV, with incidences of 18.4% and 20.4% observed in the BLV 2-mg treatment group at Weeks 48 and 96, respectively, and 30.0% at both Weeks 48 and 96 for the BLV 10-mg treatment group. Most injection site reactions were mild, resolved by Week 96, and did not require treatment interruption.
- There were no SAEs related to study drug and most SAEs were reported for no more than 1 participant overall. There were no AEs that led to premature discontinuation of study drug, and 1 death, which was assessed as not treatment related.
- Most hepatic laboratory abnormalities were Grade 1 or 2; there were 2 participants who had Grade 3 or 4 hepatic laboratory abnormalities.
- There were dose-dependent total bile salt increases observed in all groups with BLV treatment, which were asymptomatic and not related to any clinical sequelae. There does not appear to be an association between the development of pruritus and elevated bile salt levels with BLV, given that similar changes in bile salt levels were seen in those participants with or without these AEs.

3.1. Protocol Amendments and Description

7.6.2.7.4. Interim Analysis Week 96

The interim Week 96 analysis was conducted after all participants completed the visit at Week 96 or discontinued the study. Results from this analysis are presented in this report.

7.7. Changes in the Conduct of the Study or Planned Analyses

7.7.1. Changes in the Conduct of the Study

The original protocol, Protocol Version 1.0, (18 December 2018) was amended 6 times (01 February 2019, 10 April 2020, 16 September 2021, 25 April 2022, 19 October 2022, and 25 January 2023). There were local versions of the study protocol in Russia, Germany, and Sweden. Key changes to the study protocol are described below for each amendment. Complete summaries of the changes in each amendment are provided in Appendix 16.1.1.

The first study protocol version under which participants were included in the study was protocol Version 1.1, for Russia, dated 19 February 2019.

Contingency measures implemented to manage study conduct during disruption of the study as a result of COVID-19 pandemic control measures that were not included in a protocol amendment are described in the study's Risk Mitigation Plan (Appendix 16.1.1).

7.7.1.1. Country-Specific Protocol Version 1.1 for Russia

The protocol was amended on 19 February 2019 for the region of Russia to reflect the following key changes to Protocol Version 1.0:

- Information on purpose of the study, treatment duration justification, dose justification, assessment of local injection site reactions, and QOL questionnaires were added.

7.7.1.2. Protocol Version 2.0 (Amendment 1)

The protocol was amended on 01 February 2019 to reflect the following key changes:

- Inclusion and exclusion criteria were updated to include that plasma HDV RNA could be used for a participant's eligibility confirmation to be in line with routine clinical practice.
- Exclusion criteria (Criterion 1, 2, 8, 11, 20, 22, and 23) were updated to increase the participant population.
- Treatment compliance section was added.
- Text was added to the section on physical examination for assessment of local reactions at the injection sites.
- Text on local reactions at the BLV injection site was added.

- A cross-reference was added from the events of special interest to the definition of local reactions at the BLV injection site.

- For reporting of pregnancy, text was added to clarify that "if a female partner of a male participant receiving/received BLV becomes pregnant, the investigator should propose signing of the Information Sheet for pregnant partner and Informed Consent Form to the provision of information about pregnancy and its outcome" as requested by Ministry of Health of Russia and by US Food and Drug Administration recommendation.

7.7.1.3. Country-Specific Protocol Version 2.1 for Russia

The protocol was amended on 15 April 2019 for the region of Russia to reflect the following key changes to Protocol Version 2.0:

- Information on purpose of the study, treatment duration justification, dose justification, assessment of local injection site reactions, and QOL questionnaires were added.

7.7.1.4. Country-Specific Protocol Version 2.1 for Germany

The protocol was amended on 07 June 2019 for the region of Germany to reflect the following key changes to Protocol Version 2.0:

- Exclusion Criterion 8 was corrected to "patients with uncontrolled arterial hypertension: systolic blood pressure > 150 mm Hg and/or diastolic blood pressure > 100 mm Hg at screening." Exclusion Criterion 24 had the following text added: "patients receiving prohibited treatment at screening cannot be included into the study unless this treatment is withdrawn prior to randomization."

- Multiple drugs were added to the list of prohibited treatments, as follows: sulfasalazine; ezetimibe; cyclosporine; and substrates of OATPIB1/OATP1B3: atorvastatin, bosentan, docetaxel, fexofenadine, glecaprevir, glyburide (glibenclamide), grazoprevir, nateglinide, paclitaxel, paritaprevir, pitavastatin, pravastatin, repaglinide, rosuvastatin, simeprevir, simvastatin (acid), olmesartan, telmisartan, valsartan, and voxilaprevir.

7.7.1.5. Country-Specific Protocol Version 2.1 for Sweden

The protocol was amended on 20 June 2019 for the region of Sweden to reflect the following key changes to Protocol Version 2.0:

- Changes were made similar to those stated for Protocol Version 2.1 for Germany (Section 7.7.1.4).

- Additional benefit/risk information was added, as well as additional detail about the study design.

- Additional text was added to indicate that in participants for whom treatment with tenofovir tablets is contraindicated, entecavir tablets would be provided.

- Clarification was added for SAE reporting.
- Regarding the IEC and/or IRB, the following was added: “any amendment to the protocol deemed by the sponsor as ‘substantial’ will be submitted to the regulatory authority for notification and approval.”

7.7.1.6. Protocol Version 3.0 (Amendment 2)

The protocol was amended on 10 April 2020 to reflect the following key changes:

- Changes were made similar to those stated for Protocol Version 2.1 for Sweden (Section 7.7.1.5).
- The primary efficacy endpoint of undetectable HDV RNA was updated to include < LOD to provide a comprehensive definition.
- The exploratory endpoint for “clinical events (decompensation, liver-related death)” was changed to “liver-related clinical events (cirrhosis development; development or worsening jaundice, coagulopathy, ascites, hepatic encephalopathy; bleeding from esophageal varices; hepatocellular carcinoma development; liver transplantation; liver-related hospitalization: number of hospitalizations and duration of each period of hospitalization; liver related death) at all postbaseline assessments.”
- In the statistical methods, “negative PCR results for HDV RNA” was corrected to “undetectable HDV RNA.”
- In the primary analysis a technical mistake was corrected and updated to the following formula:

  H_{01}: $p_O = p_{M\ 10\ mg}$ versus H_{11}: $p_O \neq p_{M\ 10\ mg}$

  H_{02}: $p_O = p_{M\ 2\ mg}$ versus H_{12}: $p_O \neq p_{M\ 2\ mg}$
- It was specified that HBV genotyping will be performed at first positive HBV DNA.
- The clarification was made that coagulogram includes international normalized ratio.
- The endpoint of HBeAg and HBeAb status was added.
- Inclusion Criterion 6 was updated to serum albumin > 28 g/L to correct a technical mistake.
- The following text was added to Exclusion Criterion 12: “autoimmune hepatitis stigmata attributed to HDV infection in the opinion of the investigator are allowed.”
- Text was added to clarify blood sample collection and assessment of NTCP polymorphism for participants with who are nonresponders or who have viral breakthrough. The definition for viral breakthrough was also corrected.

- The following statement was added: “In case the treatment is interrupted the investigator should maintain the patient’s safety supervisions, including the ALT monitoring.”
- The clarification was made that “unused drugs” are to be returned to the investigator.
- The description of the early discontinuation visit was modified.
- It was deleted that only quantitative HDV RNA analysis can be performed at screening.
- The description for assessment of local injection reactions was expanded, including a tabular description of abnormalities.
- The exploratory endpoint of “clinical events (decompensation, liver related death)” was updated to “liver-related clinical events (cirrhosis development; development or worsening jaundice, coagulopathy, ascites, hepatic encephalopathy; bleeding from esophageal varices; hepatocellular carcinoma development; liver transplantation; liver-related hospitalization: number of hospitalizations and duration of each period of hospitalization; liver-related death) at all postbaseline assessments.”
- Text was added on AEs of special interest that included local reactions at the BLV injection site and liver-related AEs.
- Text was added to clarify collection of AE information.
- The following statement was added: "Any deviation(s) from the original statistical plan will be described and justified in protocol and/or in the final report, as appropriate.”
- Text was added to clarify pregnancy reporting requirements.
- The following instruction was added: “The sponsor will inform all the investigators of the occurrence of any suspected unexpected serious adverse reaction during the clinical conduct of the study.”
- Text was added on the HSAC activities, which included their implementation to assess all severe and SAEs related to the hepatobiliary system and other significant safety issues as considered necessary by the sponsor.

The following additions relating to the COVID-19 pandemic were also made to protocol Version 2.0 to reflect the possible influence of the COVID-19 pandemic on the study conduct:

- A statement was also added so that PDs related to COVID-19 were classified as such.
- Text was added to the benefit/risk assessment.
- A statement was made regarding supplying participants with BLV by delivery, if needed.

- For efficacy and safety assessments, the instructions for blood and urine sampling and ECG assessments were updated to assure study procedure could be performed at locations other than the participant's originally designated study site during COVID-19 pandemic.

- The instructions for informed consent were updated, allowing for initial oral informed consent over the phone, followed by email (if possible), and written informed consent at the subsequent visit, where possible.

- Provision was added for remote study monitoring.

7.7.1.7. Country-Specific Protocol Version 3.1 for Russia

The protocol was amended on 20 May 2020 for the region of Russia to reflect the following key changes to Protocol Version 2.1:

- Changes were made similar to those stated for Protocol Version 3.0 (Section 7.7.1.6).

7.7.1.8. Protocol Version 4.0 (Amendment 3)

The protocol was amended on 16 September 2021 to reflect the following key changes:

- The protocol has been amended primarily to transfer sponsorship from MYR GmbH to Gilead Sciences, Inc. and to update safety reporting procedures accordingly.

- Update to contact details, including changes to safety reporting.

7.7.1.9. Country-Specific Protocol Version 4.1 for Russia

The protocol was amended on 07 October 2021 for the region of Russia to include the changes made to generate Protocol Version 4.0 (Section 7.7.1.8).

7.7.1.10. Protocol Version 5.0 (Amendment 4)

The protocol was amended on 25 April 2022 to reflect the following key changes:

- Update to introductory sections to reflect the conditional approval of bulevirtide in the EU, other countries in Europe, and full approval in Russia for the treatment of CHD in adults with compensated liver disease.

- Update to the status of studies in the clinical development program and update to the data where applicable.

- Removal of the requirement for an additional sample to be taken for ALT for the assessment of efficacy. Rather, the result from the ALT analysis derived from the sample taken for the biochemistry will be used (Section 6.4.2). This change has been made as initially it was stated the sample taken would be frozen and shipped for analysis. However, as a result of the method validation, it transpired that ALT in serum is only stable for 7 days at −20 °C. The

unexpected short stability of ALT led to a high level of deviation between the additional ALT sample that was frozen and shipped for analysis and the ALT levels measured within the biochemistry panel.

- Text edited to permit the use of biopsy samples stored at ambient temperature, as well as frozen samples, for analysis of intrahepatic parameters. This is because collecting additional material is not practical and carries additional risks/inconveniences for the study participants; the sponsor considers it ethically unreasonable to continue sample collection.

- Language updated to include baseline HBV genotyping due to development of an ultrasensitive assay.

- Update to the definition of viral breakthrough from a confirmed increase of ≥ 2 $\log_{10}$ IU/mL HDV RNA to ≥ 1 $\log_{10}$ IU/mL HDV RNA, to expand analysis to broader participants with lower viral load increase (Section 6.4.4).

- Addition of the exploratory endpoint "HDV RNA decrease by ≥ 2 $\log_{10}$ IU/mL from baseline or undetectable HDV RNA at all postbaseline assessments."

- Update to the approach in managing participants who have missing assessment at 48 weeks for the primary endpoint as being categorized as nonresponders unless it is related to COVID19, in which case missing values will be imputed using the LOCF approach. In the key secondary analysis, participants with missing assessment at 48 weeks for undetectable HDV RNA will be handled in the same manner as the primary endpoint. Participants with a missing assessment at 48 weeks in the other secondary endpoints or exploratory endpoints will be handled as nonresponder, regardless the reason for the missing information.

- Update to the definition of TEAEs throughout and removed that incidences will be presented according to type and duration of exposure.

- Update to the definition of the PP Analysis Set to include participants with no PDs that are judged to have an impact on the analysis of the primary efficacy endpoint of combined response (or on secondary efficacy endpoint of sustained virologic response 24 at 24 weeks).

- Update of interim and final analyses to include analysis of data at Week 168.

7.7.1.11. Country-Specific Protocol Version 5.1 for Russia

The protocol was amended on 31 May 2022 for the region of Russia to include the changes made to generate Protocol Version 5.0 (Section 7.7.1.9).

7.7.1.12. Protocol Version 6.0 (Amendment 5)

The protocol was amended on 19 October 2022 to reflect the following key change:

- Update to the definitions of viral breakthrough and nonresponders, as well as the related decision tree for guiding the selection of patients for resistance testing.

7.7.1.13. Country-Specific Protocol Version 6.1 for Russia

The protocol was amended on 19 October 2022 for the region of Russia to include the changes made to generate Protocol Version 6.0 (Section 7.7.1.12).

7.7.1.14. Protocol Version 7.0 (Amendment 6)

Following Week 96 database finalization (01 November 2022), the protocol was amended on 25 January 2023 to reflect the following key changes:

- Addition of a Week 180 visit with additional assessments to allow a more standardized approach for study investigators to monitor and manage posttreatment hepatitis exacerbation.
- Update the definition of HDV RNA "undetectable" to "< lower limit of quantification (LLOQ), target not detected."
- To identify and monitor participants at risk of developing a hepatitis flare, addition of specific procedures for the management of posttreatment exacerbation of hepatitis, ie, if laboratory results indicated ALT elevations.
- Addition of an optional third liver biopsy.
- Change from Week 168 to Week 192 for the timing of an exploratory analysis.
- Clarification of details for AE/SAE reporting procedures period and liver-related clinical events.
- Addition of Appendix 2 (Monitoring Study Participants for Posttreatment ALT Elevation: Flowchart) and Appendix 3 (Unscheduled Visit for Management of Posttreatment ALT Elevations).
- Updated definition of PP Analysis Set.

7.7.1.15. Country-Specific Protocol Version 7.1 for Russia

The protocol was amended on 23 February 2023 for the region of Russia to include the changes made to generate Protocol Version 7.0 (Section 7.7.1.14).

7.7.2. Changes From Planned Analyses

There were no changes from the planned analyses specified in Protocol Version 5.0 and SAP Version 4.0.

3.2. List of Principal Investigators

MYR301: List of Principal Investigators

Study Site	
State budgetary institution of health care of Moscow region “Moscow regional research clinical institute after M.F. Vladimirsky" 61/2 Shchepkina str., Moscow, Russia, 129110	
Federal Budget Institute of Science "Central Research Institute for Epidemiology" of Federal Service on Consumers Rights Protection and Human Well-Being Surveillance 3a Novogireevskaya Street, Moscow, Russia, 111123	
the State Budgetary Healthcare Institution of Stavropol region “Stavropol Regional Clinical Hospital” 208, Lermontova str. Stavropol, Russia, 355002	
FSBI National Research Medical Center for Phthisiopulmonology and Infectious Diseases of the Ministry of Health of the Russian Federation 4, bld.2, Dostoevskogo str., Moscow, Russia, 127473	
Medical Company “Hepatolog” LLC 36A, Serdobskaya str., Samara, Russia, 443063	
Federal State Budgetary Educational Institution of Higher Professional Education “South Ural State Medical university” of the Ministry of Healthcare of the Russian Federation 2 Cherkasskaya str., Chelyabinsk, Russia, 454052	

Study Site	
LLC Clinic of Modern Medicine 2/1, Ploschad Pobedy, Moscow, Russia, 121170	
State budgetary institution of health care "Specialized clinical infectious diseases hospital" of the Ministry of health of Krasnodar region 204 Mitrofana Sedina str., Krasnodar, Russia, 350015 State budgetary institution of health care "Specialized clinical infectious diseases hospital" of the Ministry of health of Krasnodar region 204 Mitrofana Sedina str., Krasnodar, Russia, 350015	
Heidelberg University Hospital, Departament of Gastroenterology, Infectious Diseases, Intoxication Im Neuenheimer Feld 410, Heidelberg, Germany, 69120	
Universitätsklinikum Hamburg-Eppendorf Medizinische Klinik Studienambulanz Hepatologie Martinstraße 52 (Haus O28, EG, R39) Hamburg, Germany, 20246	
Klinik für Gastroenterologie, Hepatologie und Endokrinologie, Medizinische Hochschule Hannover 1 Carl-Neuberg-Straße, Hannover, Germany, 130625 Klinik für Gastroenterologie, Hepatologie und Endokrinologie, Medizinische Hochschule Hannover 1 Carl-Neuberg-Straße, Hannover, Germany, 130625	

Study Site	
Universitätsklinikum Essen (AoR), Klinik für Gastroenterologie und Hepatologie Hufelandstraße 55, Essen, Germany, 45147 Universitätsklinikum Essen (AoR), Klinik für Gastroenterologie und Hepatologie Hufelandstraße 55, Essen, Germany, 45147 Universitätsklinikum Essen (AoR), Klinik für Gastroenterologie und Hepatologie Hufelandstraße 55, Essen, Germany, 45147	
Universitätsklinikum Frankfurt Medizinische Klinik 1 Haus 11, 3 OG Theodor-Stern-Kai 7D, Frankfurt am Main, Germany, 60596	
Azienda Ospedaliero-Universitaria di Modena Ospedale Civile S.Agostino Estense di Baggiovara Unità Operativa Complessa di Medicina Interna Metabolica Via Pietro Giardini 1355, Baggiovara (MO), Italy, 41126	
U.O Epatologia - Azienda Ospedaliero Universitaria Pisana Via Paradisa, 2, Pisa, Italy, 56124	
Division of Gastroenterology and Hepatology, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico 35 Via Francesco Sforza, Milano, Italy, 20122	

Study Site		
Karolinska University Hospital Huddinge 141 86, Stockholm, Sweden		
NYU Langone 550 First Ave, New York, NY, USA, 10016		

MYR 301: Number of Subjects Enrolled Per Country

Country	No. of Subjects Enrolled
Russia	85
Germany	27
Italy	24
Sweden	14
US	0