CLINICAL STUDY PROTOCOL

Study Title:	A Multicenter, Open-label, Randomized Phase 3 Clinical Study to Assess Efficacy and Safety of Bulevirtide in Patients with Chronic Hepatitis Delta
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Protocol Identification:	MYR301
Version Number and Date:	Version 5.0 dated 25 April 2022
EudraCT number:	2019-001213-17
ClinicalTrials.gov Identifier:	NCT03852719

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SIGNATURE PAGE 1 (SPONSOR)

Protocol Title: A Multicenter, Open-label, Randomized Phase 3 Clinical Study to Assess Efficacy and Safety of Bulevirtide in Patients with Chronic Hepatitis Delta.

The signature below constitutes approval of this protocol by the signatory and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol.

[*See appended electronic signature*]

Signature: _____ Date: _____/_____/_____

PPD day/month/year

Medical Monitor, Clinical Development

Gilead Sciences, Inc.

SIGNATURE PAGE 2 (PRINCIPAL INVESTIGATOR)

Protocol Title: A Multicenter, Open-label, Randomized Phase 3 Clinical Study to Assess Efficacy and Safety of Bulevirtide in Patients with Chronic Hepatitis Delta.

The signature of the below constitutes agreement of this protocol by the signatory and provides the necessary assurance that this study will be conducted at his/her investigational site as outlined in the protocol, Good Clinical Practice, and all international and local regulations that apply for this study including all statements regarding confidentiality.

Institution title: _____

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Investigator's name: _____

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Date: _____

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Central laboratories and other contacts:	Central laboratories, their addresses and other contact information are provided in a contact list. This list will be regularly updated as needed; the most current version is available in the sponsor's trial master file and site file.

LIST OF ABBREVIATIONS

AASLD	American Association for the Study of Liver Diseases
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse Event of Special Interest
ALT	Alanine aminotransaminase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransaminase
BMI	Body mass index
CD	Cluster determinant
cccDNA	Covalently closed circular DNA
CHB	Chronic hepatitis B
CHD	Chronic hepatitis delta
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CRA	Clinical research associate
CRO	Contract research organization
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450 enzyme
DNA	Deoxyribonucleic acid
EASL	European Association for the Study of the Liver
EC_{50}	Half-maximal effective concentration
ECG	Electrocardiogram
eCRF	Electronic case report form
ELISA	Enzyme-linked immunosorbent assay
EOS	End of study
EOT	End of treatment
EQ-5D	EuroQol 5-Dimentions
EU	European Union
FAS	Full analysis set
FSS	Fatigue Severity Scale
FU	Follow-up
GCP	Good Clinical Practice
GGT	Gamma glutamyltransferase
HBeAg	Hepatitis B virus e antigen
HBsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HDAg	Hepatitis delta antigen
HDV	Hepatitis delta virus

HIV	Human immunodeficiency virus
HQLQ™	The Hepatitis Quality of Life Questionnaire™
HSAC	Hepatic Safety Adjudication Committee
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional Review Board
LOCF	Last observation carried forward
LoD	Limit of detection
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed effect repeated measurement models
NCI	National Cancer Institute
NTCP	Sodium-taurocholate cotransporting polypeptide
OATP	Organic anion transporting polypeptide
PCR	Polymerase chain reaction
PI	Principal Investigator
PP	Per-protocol set
PR (interval)	Electrocardiographic interval occurring between theonset of the P wave and the QRS complex representing time for atrial and ventricular depolarization, respectively
PT	Preferred term
QRS	Electrocardiographic deflection between the beginning of the Q wave and termination of the Swave, representing time for ventricular depolarization
QT (interval)	Electrocardiographic interval between the beginningof the Q wave and termination of the T wave, representing the time for both ventricular depolarization and repolarization to occur
QTc	QT interval corrected for heart rate
RBC	Red blood cell
RNA	Ribonucleic acid
REML	Restricted maximum likelihood
RR (interval)	Electrocardiographic interval representing the timemeasurement between the R wave of one heartbeatand the R wave of the preceding heartbeat
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneously
SOC	System Organ Class
SUSAR	Suspected unexpected serious adverse reaction
SVR	Sustained virological response
TDF	Tenofovir disoproxil fumarate
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
US, USA	United States, United States of America
WBC	White blood cell

SYNOPSIS

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
Protocol Identification:	MYR301
Study sites:	Approximately 24 study sites in approximately 6 countries globally which may include Germany, Russia, Italy, Georgia, United States (US), and Sweden
Phase of Development:	Phase 3
Objectives:	**Primary:** The primary objective of this study is to evaluate the efficacy of bulevirtide administered subcutaneously for 48 weeks at a dose of 2 mg or 10 mg once daily for treatment of chronic hepatitis delta in comparison to delayed treatment. **Secondary:** • To evaluate optimal treatment duration • To assess the safety of bulevirtide. CCI [redacted]
Methodology:	This is a randomized, open-label, parallel group multicenter Phase 3 study. Randomization is stratified by the presence of liver cirrhosis (no/yes).
Diagnosis and Main Criteria for Inclusion:	Adult male and female with chronic HDV infection and elevated alanine aminotransferase (ALT) at Screening.
Treatments: Arm A (comparator): Arm B: Arm C:	 Observation for 48 weeks followed by bulevirtide 10 mg/day for 96 weeks and further follow-up period for 96 weeks. Bulevirtide 2 mg/day for 144 weeks with a further follow-up period of 96 weeks Bulevirtide 10 mg/day for 144 weeks with a further follow-up period of 96 weeks

Mode of Administration:	The study is open-label. **Bulevirtide 10 mg**: two injections of bulevirtide each 5 mg. Two injections are performed one after another without time lag between injections. These injections are performed daily, every 24±1 hours. **Bulevirtide 2 mg**: one injection of 2 mg bulevirtide. Injection is performed daily, every 24±1 hours
Concomitant medication:	Nucleoside/nucleotide analogue indicated for the treatment of chronic HBV infection should be given during screening, treatment and/or follow-up period if required for control of the underlying chronic HBV infection, according to the current clinical guidelines (European Association for the Study of the Liver [EASL] and American Association for the Study of Liver Diseases [AASLD]). The sponsor will be providing tenofovir (tablets) if the drug cannot be made available for patients through routine medical care. In patient in whom tenofovir is contraindicated, entecavir (tablets) will be provided.
Criteria for Evaluation:	*Primary Efficacy Endpoint* Combined response at Week 48. Combined response is defined as fulfilment of two conditions simultaneously: — Undetectable (< limit of detection [LoD]) HDV RNA or decrease by ≥ 2 $\log_{10}$ IU/mL from baseline — ALT normalization *Secondary Efficacy Endpoints* • Undetectable HDV RNA at Week 48 • ALT normalization at Week 48 • Undetectable HDV RNA 24 weeks after scheduled end of treatment (sustained virological response) • Undetectable HDV RNA 48 weeks after scheduled end of treatment (sustained virological response) • Change from baseline in liver stiffness as measured by elastography at Weeks 48, 96, 144, 192, and 240 CCI [redacted]

Criteria for Evaluation (continued:	CCI • Liver related clinical events (such as, but not limited to, 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 hospitalization; liver related death) at all postbaseline assessments CCI *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 PR, 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) CCI *Pharmacokinetic variables* • Plasma concentration of bulevirtide

	Other variables [redacted] • Sodium-taurocholate cotransporting polypeptide (NTCP) polymorphism [redacted] • Hepatitis B virus e antigen (HBeAg) and HBeAg antibodies status at all postbaseline assessments (for patients with positive HBeAg at screening) • 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; semi-quantitative analysis of HBsAg and hepatitis delta antigen (HDAg) with immunohistochemistry)
Statistical Methods:	**Sample size** The primary analysis of the study is the separate comparisons of bulevirtide 2 mg and bulevirtide 10 mg treatment with delayed treatment after a period of 48 weeks. The primary endpoint is defined as the response rate at Week 48 measured by undetectable HDV RNA or a decrease by ≥ 2 $\log_{10}$ IU/mL from baseline combined with normal ALT values within the reference range. The overall significance level will be 0.05. An interim analysis will be performed on the response rates at Week 24. To account for the repeated analysis of response the nominal two-sided significance level will be split among the time points with 0.01 for 24 weeks leaving 0.04 for 48 weeks. At each time point the bulevirtide doses will be compared with delayed treatment in terms of a hierarchical testing procedure starting with the higher dose at the respective adjusted two-sided significance levels. The expected response rates at 48 weeks for the bulevirtide 2 mg and 10 mg doses are 45% or greater. The conservative expectation for the delayed treatment response rates are 8% or less. These assumptions are based on results from preceding Phase 2 study (MYR202). With a sample size of 47 patients per treatment group a Fisher's exact test with a 0.04 two-sided significance level will have 97.8% power to detect this difference between the bulevirtide 10 mg and the delayed treatment proportions and between the bulevirtide 2 mg and the delayed treatment proportions. The power to reject both null hypotheses simultaneously will be 95.6%. This sample size will be slightly increased to 50 patients per treatment group to account for a few potential early withdrawals before exposure. Hence 150 patients will be randomized. **Analysis populations** • Enrolled set: All patients screened and enrolled into this study. • Randomized set: All enrolled and randomized patients.

Statistical Methods (continued):	• Full analysis set (FAS): All patients randomized to delayed treatment arm or randomized to bulevirtide and received bulevirtide at least once after randomization. • Per-protocol (PP) set: All patients of the FAS for whom no protocol deviations are judged to have an impact on the analysis of the primary efficacy endpoint of combined response (or on secondary efficacy endpoint of sustained virological response [SVR24] at follow-up Week 24 [FU-24], ie study Week 168). Details will be specified in the statistical analysis plan (SAP) and final decision on exclusion from PP set will be made in a data review meeting before data base lock. • Safety population: All patients randomized to delayed treatment arm or randomized to bulevirtide and received bulevirtide at least once after randomization. **Demographic and baseline measurements** All demographic and background characteristic variables will be summarized by treatment group and overall to describe the study population. The data will be presented for all patients in the FAS. **Analysis of efficacy** Continuous variables will be summarized in terms of descriptive statistics including number of observations, mean, standard deviation, minimum, maximum and quartiles. Categorical variables will be summarized in terms of frequencies and percentages. Where data are collected over time, both the observed data and the change from baseline will be summarized by treatment group at each time point. Primary analysis: The primary endpoint of this study is the response rates at Week 48 where response is defined as undetectable HDV RNA or decrease by ≥ 2 $\log_{10}$ IU/mL from baseline combined with ALT level within reference range. Two two-sided Fisher tests at an overall significance level of 0.05 will be performed to sequentially test the hypotheses H_{01}: $p_O = p_{M10mg}$ vs. H_{11}: $p_O \neq p_{M10mg}$ H_{02}: $p_O = p_{M2mg}$ vs. H_{12}: $p_O \neq p_{M2mg}$ At each time point where p_O, p_{M2mg}, and p_{M10mg} are the expected response rate for delayed treatment group, bulevirtide 2 mg and bulevirtide 10 mg, respectively. Patients with missing assessment at 48 weeks in the primary endpoint will be handled as non-responder unless it is related to COVID-19 in which case missing values will be imputed using the last observation carried forward (LOCF) approach. In terms of a hierarchical testing procedure, the second null hypothesis will not be rejected if the first null hypothesis could not be rejected. CIs with confidence probability adjusted to the respective significance levels using exact unconditional confidence limits based on the score statistic will be presented for the rate differences. Clopper-Pearson 95%-CIs will be calculated for the single rates.

Statistical Methods (continued):	An interim analysis will be performed on the response rates at Week 24. To account for the repeated analysis of response the nominal two-sided significance level will be split among the time points with 0.01 for 24 weeks and 0.04 for 48 weeks. The primary analysis will be based on the FAS. The analysis will be repeated for the PP set and in case of differences between the FAS and the randomized set also for the randomized set to assess consistency and robustness of results. Due to the expected low number of responders in delayed treatment group the analysis will not be stratified by covariables. The effect of region and the presence of liver cirrhosis will be analyzed descriptively. <u>Key secondary analysis</u> The proportion of patients with undetectable HDV RNA at Week 48 is the key secondary endpoint and will be used to test differences between the bulevirtide doses and hence evaluate the dose response relationship. Patients with missing assessment at 48 weeks in undetectable HDV RNA will be handled in the same way as the primary efficacy endpoint described above. A two-sided Fisher tests will be performed to test the hypotheses H_{03}: $r_{M2mg} = r_{M10mg}$ vs. H_{13}: $r_{M2mg} \neq r_{M10mg}$ where r_{M2mg}, r_{M10mg} are the expected rates of patients with undetectable HDV RNA for bulevirtide 2 mg and bulevirtide 10 mg, respectively. Continuing the hierarchical testing procedure used for the primary endpoint this test will only be performed if both primary null hypotheses have been rejected. Otherwise null hypothesis H_{03} will not be rejected. To maintain control of the family-wise error rate the same nominal levels of significance will be employed that was used for the primary analyses. CIs with confidence probability adjusted to the respective significance levels using exact unconditional confidence limits based on the score statistic will be presented for the rate differences. Clopper-Pearson 95%-CIs will be calculated for the single rates. The same methods will be applied at the interim analysis on response at Week 24. <u>Other secondary analyses</u> All other efficacy data will be analyzed descriptively. Rates of patients with ALT normalization at Week 48, undetectable HDV RNA at 24 and 48 weeks after scheduled end of treatment (sustained virological response) will be analyzed analogously to the primary endpoint in the framework of explorative analysis without adjusting for multiple testing. Change from baseline in liver stiffness as measured by elastography will be analyzed in a mixed effect repeated measurement model (MMRM) with fixed-effect factors treatment, region, presence of cirrhosis, visit and treatment-by-visit interaction and the baseline values as covariable. CIs will be based on estimated means (least square means) and corresponding t-

	statistics. Restricted maximum likelihood (REML) will be employed to fit the model for primary analysis. Within- patient variation will be modeled as random effect with unstructured covariance structure. The Kenward-Roger (35) approximation will be used to estimate the denominator degrees of freedom. If the model still fails to converge, the model will be fit using covariance matrices of the following order specified by a decreasing number of covariance parameters until convergence is met: heterogeneous Toeplitz, heterogeneous autoregressive, Toeplitz, and autoregressive. CCI [redacted] [redacted] **Analysis of safety** Adverse events Adverse events will be coded using MedDRA and will be presented by primary System Organ Class (SOC) and Preferred Term (PT). The analysis will focus on the treatment-emergent AEs (TEAE), ie, AEs which started or worsened after randomization (delayed treatment group) or after start of treatment (bulevirtide groups) and no later than 30 days after permanent discontinuation of treatment. The frequency of TEAEs will be summarized by incidences. In these summaries, each patient will be counted only once within each PT. Frequencies of TEAEs will also be presented by relationship to study treatment and by maximum severity. Additional analyses will be performed for serious AE (SAE), treatment-emergent SAE (TESAE), and AEs leading to discontinuation. Vital signs Vital signs will be described by summary statistics for measured values and changes from baseline by visit. Laboratory parameters Laboratory parameters will be described by summary statistics for measured values and changes from baseline by visit. The clinical assessment of laboratory variables (abnormal high/ clinically relevant, abnormal high/not clinically relevant, within normal limits, abnormal low/not clinically relevant, abnormal low/clinically relevant) will be tabulated by visit for each clinical laboratory analyte in frequency tables. Additionally, for each laboratory parameter shifts in assessments from baseline to Week 48 and Week 96 visit will be presented (shift tables). Electrocardiogram The ECG assessment summary categories will be tabulated by visit. Additionally, shifts in assessments from baseline to visits will be presented (shift tables). Descriptive summaries of actual values and changes from baseline will be presented for ECG measures of PR interval, QRS interval, QT interval, QT-interval corrected for heart rate (QTc, Bazett), and heart rate by visit.

	Also, the number and percent of patients in each treatment group with QTc values 451 - 480 ms, 481 - 500 ms or > 500 ms and the number and percentage of patients in each treatment group who experienced a change versus baseline > 30 ms or a change > 60 ms will be presented by visit. Other safety assessments The number and percentages of patients with normal/abnormal findings in physical examinations as well as with production of bulevirtide antibodies will be presented by visit.

Table 1. Schedule of Events

Study phase V (Visit) / W (Week) / D (Day) Procedures [1]	Screening	144-week Treatment phase (app. 3 years)*					96-week Follow-up phase		
	SCR	V1	V2 – V7	V8	V9 – V18	V19	FU 1	FU 2-5	FU 6 / EOS
	D-28 to D-1 **	W0 / D1	± 2 days: W4, W8, W16, W24, W32, W40	± 2 days: W48	± 2 days: W52, W56, W64, W72, W80, W88, W96, W108, W120, W132	± 2 days: W144	± 3 days: W148	±7 days W156, W168, W192, W216	±7 days W240
CLINICAL AND INSTRUMENTAL EVALUATIONS									
Informed consent [2]	X								
Demographics [3]	X								
Medical history, prior therapy [4]	X								
Weight, height, BMI (height and BMI at SCR only)	X	X	X	X	X	X	X	X	X
Physical examination [5]	X	X [6]	X	X	X	X	X	X	X
Assessment of local reactions at the bulevirtide injection site[7]		X	X	X	X	X	X		
Vital signs [8]	X	X	X	X	X	X	X	X	X
12-lead electrocardiogram (ECG)	X		X (W8, W24)	X	X (W72, W96, W120)	X		X (W192)	X
Abdominal ultrasound	X								
Transient elastometry (FibroScan)	X			X	X (W96)	X		X (W192)	X
Breath alcohol test	X	X							
Inclusion/Exclusion criteria	X	X							
Adverse events (including liver related clinical events starting from randomization)	X (SAE only)	X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X	X
Randomization [9]		X							

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TREATMENT DISPENSING/RETURN									
Bulevirtide [10]		X [7, 10]	X [7, 10]	X [10]	X [10]	X [10]			
Treatment compliance assessment			X[7]	X	X	X			
Patient Diary Dispensing/Review/Collection		X[7]	X[7]	X	X	X			
CCI									
LOCAL LABORATORY/STUDY SITE									
Urine pregnancy test [11]	X	X	X	X	X	X	X	X	X
Urine drug screening test	X								
ANALYSES PERFORMED IN CENTRAL LABORATORY / SAMPLES TO BE SENT TO CENTRAL LABORATORY AT ONCE									
Serology (anti-HIV, anti-HCV, anti-HDV)	X								
HCV RNA (if anti-HCV positive at SCR)	X								
HBeAg and HBeAg antibodies	X								
Urinalysis	X	X [6]	X [12]	X	X [12]	X		X [12]	X
Hematology [13]	X	X [6]	X	X	X	X	X	X	X
Biochemistry (full panel) [14]	X	X [6]	X (W24)	X	X (W72, W96, W120)	X			X
Biochemistry (abbreviated panel) [15]			X (W4, W8, W16, W32, W40)		X (W52, W56, W64, W80, W88, W108, W132)		X	X	
Coagulogram [16]	X	X [6]	X (W8, W24, W40)	X	X (W64, W80, W96, W108, W120, W132)	X		X (W168, W192, W216)	X
Total blood bile salts		X	X	X	X	X	X	X	X

Study phase V (Visit) / W (Week) / D (Day) Procedures [1]	Screening	144-week Treatment phase (app. 3 years)*					96-week Follow-up phase		
	SCR	V1	V2 – V7	V8	V9 – V18	V19	FU 1	FU 2-5	FU 6 / EOS
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Alpha-fetoprotein test	X								
Vitamin D		X	X (W24)	X	X (W72, W96, W120)	X		X (W168, W192)	X
HBV DNA for pts. not receiving nucleoside/nucleotide analogues	X								
Serum alpha-2-macroglobulin		X		X	X (W96)	X		X (W168)	X
ANALYSIS PERFORMED IN CENTRAL VIROLOGY LABORATORY / SAMPLES TO BE SENT TO CENTRAL LABORATORY AT ONCE									
HDV RNA	X								
ANALYSIS PERFORMED IN CENTRAL VIROLOGY LABORATORY / SAMPLES TO BE STORED AT SITE									
CCI									
HDV RNA		X	X	X	X	X	X	X	X
CCI									
CCI									
HBeAg and HBeAg antibodies [18]		X		X	X (W96)	X			X
ANALYSIS PERFORMED IN CENTRAL LABORATORY / SAMPLES TO BE STORED AT SITE									
CCI									
NTCP polymorphism[20]		X							
Resistance test [21] (HBV genome sequencing, phenotypic assay and HDV genome sequencing)		X [21]	X [21]	X[21]	X[21]	X [21]	X [21]	X [21]	X [21]
Pharmacokinetics		X [22]	X [22]	X [22]	X [22]	X [22]			

Study phase V (Visit) / W (Week) / D (Day) Procedures [1]	Screening	144-week Treatment phase (app. 3 years)*					96-week Follow-up phase		
	SCR	V1	V2 – V7	V8	V9 – V18	V19	FU 1	FU 2-5	FU 6 / EOS
	D-28 to D-1 **	W0 / D1	± 2 days: W4, W8, W16, W24, W32, W40	± 2 days: W48	± 2 days: W52, W56, W64, W72, W80, W88, W96, W108, W120, W132	± 2 days: W144	± 3 days: W148	±7 days W156, W168, W192, W216	±7 days W240
Liver biopsy	X [23]			X [24]					

*Visits at W0 – W8 and W48-W56 are performed every 28±2 days; at W8 – W48 and W56-W96: every 56±2 days; at W96 – W144: every 84±2 days
**Screening can be shorter than 28 days as soon as eligibility of patient is confirmed.

1. Detailed description of all study procedures can be found in Section 6 of this protocol.
2. Signed and dated informed consent must be obtained before any procedure specific to this protocol.
3. Demographics include: date of birth, sex, race, smoking/alcohol/drugs abuse history and current use.
4. Information about diseases, conditions and surgeries related to the liver is collected for a lifelong period; Information about other diseases, conditions and surgeries is collected if they have occurred within 5 years before the Screening or regardless of the time if they are considered to be relevant by investigator. All previous treatment for viral hepatitis should be recorded. Prior therapy for other diseases is collected for therapies that patient receives currently and therapies that were discontinued within 3 months before Screening.
5. A complete physical examination is performed at Screening (SCR), Randomization (V1), Week 24, Week 48, Week 96, and Week 144. A complete physical examination includes evaluation of general appearance, skin, head, eyes, ears, nose and throat, lymph nodes, respiratory, cardiovascular, gastrointestinal including hepatobiliary assessment, musculoskeletal, endocrine system, nervous systems, and urogenital system. At all other visits, a symptom directed physical examination is performed.
6. If at Screening was done over 14 days ago.
7. Arm A: starting from W48.
8. Vital signs include body temperature, heart rate, and blood pressure. Vital signs are measured as indicated in Table 1 and when clinically indicated.
9. Patients eligible for the study are randomized after completion of all procedures scheduled for Screening and Day 1 (except study drug administration, patient diary dispensing and assessment of adverse events, sample collection for pharmacokinetics) and confirmation of subject's eligibility.
10. Patients should be instructed NOT to administer study drug at home at days of visits to study sites. At these days study drug is administered at study site in accordance with schedule of events for assessment of CCI [redacted] and pharmacokinetics of the study drug.
11. Only for women of childbearing potential.
12. Urinalysis is not needed at V2 (W4), V9 (W52), and FU3 (W168).
13. Hematology includes hemoglobin, hematocrit, reticulocytes, RBC, platelet count, WBC with differential (absolute counts and percentage for neutrophils, eosinophils, basophils, monocytes, and lymphocytes).
14. Subjects must attend study sites after fasting for at least 9 hours (water and concomitant medications are permitted) for the purpose of conducting the biochemistry. Full biochemistry includes: total protein, albumin, ALT [this sample will be used to obtain ALT results for efficacy assessment as described in Section 6.5.4], AST, GGT, P-amylase, alkaline phosphatase, lipase, total bilirubin, direct bilirubin, total cholesterol, creatinine, urea, glucose, potassium, sodium, chloride, phosphorus, and CRP.
15. Subjects must attend study sites after fasting for at least 9 hours (water and concomitant medications are permitted) for the purpose of conducting the biochemistry. Abbreviated biochemistry includes: albumin, ALT [this sample will be used to obtain ALT results for efficacy assessment as described in Section 6.5.4], AST, GGT, total bilirubin, direct bilirubin, creatinine, lipase, P-amylase, CRP.
16. Coagulogram includes prothrombin time, INR and aPTT.

CCI [redacted].

18. Collection and testing of HBeAg and HBeAg antibodies only if patient is HBeAg positive at SCR.

CCI [redacted]

20. Blood samples for determination of NTCP polymorphism are collected at Day 1 for all the patients. NTCP polymorphism will be performed in central laboratory for patient who are either non-responders or have viral breakthrough as detailed in Section 6.4.4 of this protocol.
21. Dedicated samples for phenotypic assay are collected only at Day 1. For other resistance tests (HBV genome sequencing and HDV genome sequencing) and phenotypic assay at the other timepoints back-up virology samples are used. Full resistance tests are performed in patients for whom results of HDV RNA testing in central laboratory indicate lack of response (non-responders) or viral breakthrough as detailed in Section 6.4.4 of this protocol.
22. During first 48 weeks pharmacokinetics samples are taken only for Arms B and C. One sample at each visit 1h±15 min post bulevirtide dose.
23. At Screening liver biopsy is performed after confirmation of eligibility. If a liver biopsy was performed within 1 year prior to Screening, and a patient can provide biopsy records and appropriate biopsy specimens, the available specimens can be used for the baseline evaluation and biopsy at Screening is not required. Otherwise liver biopsy at screening is performed if feasible provided that patient is considered to be eligible after the review of all eligibility criteria.
24. Liver biopsy should be performed within ± 7 days from the date of the visit for patients who do not have medical contraindications for the procedure. If baseline liver biopsy samples are not available (were not provided to central laboratory or were considered as non-evaluable by central laboratory) subsequent liver biopsy should not be performed.

1. INTRODUCTION

1.1. Hepatitis Delta

Hepatitis delta is liver inflammation caused by infection with hepatitis delta virus (HDV), which requires the presence of the hepatitis B virus surface antigen (HBsAg) for its complete replication and transmission. HDV is a hepatotropic virus with a small RNA genome also containing the hepatitis delta antigen (HDAg). HDV is necessarily associated with hepatitis B virus (HBV) infection, as HDV ribonucleoprotein buds through the HBsAg secretory pathway. The HDV genome is a single-stranded RNA of 1,680 bases; it has historical homology with viroids or plant virus satellite RNA [1]. The HDAg consists of 2 isoforms, the small 24 kD protein which is required for the replication, and the larger 27 kD protein which is needed for virion formation [2]. There are eight genotypes of HDV, while virus of genotype 1 is the most common in the world and in Europe [3].

In general, HDV is a highly pathogenic virus causing acute and chronic liver disease. Although benign course of the disease has been described [4], patients with chronic hepatitis delta (CHD) usually have progressive liver disease leading to compensated or decompensated cirrhosis. Evidence was reported in the literature, that unlike HBV, HDV can be associated with direct cytotoxicity which may hasten the fibrosis process [5, 6]. However, the immune system plays the major role in the clearance of the infected hepatocytes; levels of HDV viremia are not directly associated with histological changes [7]. There is no histological feature distinctive of hepatitis delta from other types of viral hepatitis. Biopsy specimens of patients with CHD exhibit portal and periportal inflammation, fragmentary necrosis, often accompanied by fibrosis and cirrhosis. Marked intraglobular infiltration by mononuclear cells and degenerative changes in hepatocytes [8] is seen. Clinically, HDV may cause acute or fulminant hepatitis, chronic infection may lead to asymptomatic carrier state or evolve to rapidly progressive chronic liver disease.

Chronic hepatitis delta develops in 70-90% of patients with HDV superinfection. The liver disease associated with HDV runs a more progressive course than chronic hepatitis B (CHB) and may lead to cirrhosis within 2 years in 10-15% of patients [9]. Hepatitis delta is considered the most severe form of viral hepatitis in humans [10], and is associated with progression of liver disease, development of cirrhosis and decompensation [11, 12].

A study conducted with a patient cohort observed for a long time showed a clear trend towards a decreased survivability of hepatitis B virus e antigen (HBeAg)-negative patients with HDV, compared to patients with HBV monoinfection [13]. In endemic populations with HDV infection, liver disease is a serious medical problem. In the study performed in Italy in 1987, anti-HDV antibodies were detected in 40% of patients with hepatic cirrhosis. Despite the fact that in 2000 the percent was reduced to 11% [14], HDV infection continues to be a huge burden for health care services. A longitudinal study has shown that 20% of CHD patients develop a liver-related first time event during the median follow-up time of 4 years, versus only 8.5% of HBV monoinfected patients [15]. At baseline, 19.8% of the patients of this cohort had cirrhosis, compared to 7.3% of CHB patients. HDV was a cause of death for 60% of patients in a 28-year study from Italy [16]. HDV co-infection is associated with faster progression to fibrosis and cirrhosis, earlier onset of hepatic complications and likelihood of liver transplantation [17-19].

Liver cirrhosis and cancer occur 10-15 years earlier in HBV/HDV co-infection and the 5-year mortality of co-infected individuals is twice that of HBV monoinfection [20]. Chronic HDV infection causes cirrhosis and hepatocellular carcinoma (HCC) with annual rates of 4% and 2.8%, respectively [16].

On average, 5-10% of HBsAg-positive patients admitted to tertiary centers in Europe test positive for HDV. The calculation of total number of people affected by CHD in the European Union (EU) has yielded the estimate of 145,000 persons. Accounting for EU population of 505,665,700 (2013), the expected prevalence of HDV among EU citizens, under these assumptions, is 2.9 in 10,000, where best- and worst-case assumptions (the limits of the 95 per cent credibility interval) are 1.6 and 4.7 in 10,000, respectively. The worst-case scenario is below the Orphan Drug designation threshold of 5 in 10,000 people affected by this condition.

The estimated HDV prevalence in the United States (US) is based on limited data from literature. A recent study utilizing data of a tertiary center database revealed HDV prevalence of 8% among HBsAg carriers [21]. 11% of injection drug users were tested positive for HDV in Baltimore; in those with chronic HBV infection, 50% were HDV positive [22]. On an average, 5-10% of HBsAg-positive patients who admit to tertiary centers are tested positive for HDV. The calculation of total number of people affected by CHD in the US has yielded the estimate of 63,800 persons (worst-case scenario). This is below the Orphan Drug designation threshold of 200,000 people affected by the condition.

1.2. Treatment Options for Hepatitis Delta

The therapeutic options for HDV co-infected patients have been very limited. Previously, according to the European Association for the Study of the Liver (EASL) 2017 Clinical Practice Guidelines on the management of HBV infection [23], pegylated interferon alpha was the only available drug that has been proven to have some antiviral efficacy against chronic HDV infection [24, 25]. Studies applying pegylated interferon alpha showed on-treatment virologic response rates of about 17-47% [24]. The rate of undetectable HDV RNA 24 weeks after treatment cessation was, however, rather low (approximately 25%), and late relapses of HDV replication beyond Week 24 after stopping therapy occurred in more than 50% of the responder patients, thus challenging the concept of sustained virologic response in HDV-HBV co-infection [26]. Hence, long-term follow-up HDV RNA monitoring is recommended for all treated patients as long as HBsAg is present in serum. HBsAg loss may develop in the long-term follow-up in approximately 10% of pegylated interferon alpha treated patients and can be taken as a marker of cure for HDV infection [26, 27].

Several studies tried to increase efficacy by increasing treatment duration [28, 29]. However, clear evidence is lacking to confirm that this approach is beneficial for most chronically HDV infected patients. Even after 96 weeks of pegylated interferon alpha therapy, alone or in combination with tenofovir, 24-week post-therapy relapses occurred in 36-39% of the patients with on-treatment response [30].

Neither nucleoside/nucleotide analogues nor ribavirin showed significant effects on HDV RNA levels in patient with HDV infection [24]. Although HDV is often the predominant virus in this co-infection, considerable fluctuating activity of HDV and HBV or both viruses, including

alternating predominance can be seen during the natural history of this chronic co-infection [24]. nucleoside/nucleotide analogue treatment is recommended for those patients with HBV DNA levels being persistently above 2,000 IU/mL, and might be considered in order to block residual HBV replication in those with advanced liver disease. In patients with decompensated liver disease, pegylated interferon alpha should not be used and these patients should be evaluated for liver transplantation. Nucleoside/nucleotide analogue should be considered in all patients with decompensated disease if HBV DNA is detectable [23].

Thus, there is an urgent unmet medical need for new medications to treat chronic HDV infection as the success rate of currently available de-facto treatment is low. Several candidates are being evaluated in clinical trials: drugs inhibiting the release of HBsAg (nucleic acid polymers), inhibitors of the prenylation of the large HDAg and bulevirtide – currently the only representative of a novel class of HBV/HDV entry inhibitors [23].

1.3. Background on Bulevirtide

1.3.1. Description of the Study Drug

Bulevirtide is a myristoylated N-terminal and amidated C-terminal 47-amino acid lipopeptide. The drug substance is available as acetate salt. Drug formulation is lyophilized powder for injections. Bulevirtide is supplied in sterile vials. The vial content has to be reconstituted in 1 mL sterile water for injection prior to administration. Bulevirtide is given by subcutaneous injection (SC).

Bulevirtide blocks the entry of HBV into hepatocytes by binding to and inactivating an essential HBV/HDV entry receptor described as sodium-taurocholate cotransporting polypeptide (NTCP) receptor. Bulevirtide acts at a post attachment step probably misdirecting the entry route of HBV/HDV to an unproductive cellular pathway.

Bulevirtide (2 mg) is conditionally approved under the brand name Hepcludex® in the EU and other countries in Europe and is fully approved as Myrcludex B® in Russia for the treatment of CHD in adults with compensated liver disease.

1.3.2. Summary of Clinical Data

Six clinical studies have been conducted on bulevirtide so far and 2 clinical studies are currently ongoing:

- Study MYR101: An Open-Label, Single Center, Phase 1a Clinical Trial to Evaluate the Safety, Tolerability, and Pharmacokinetics of Myrcludex B in Healthy Volunteers *[completed]*

- Study MYR102: Assessment of a Potential Drug-Drug Interaction Between the Novel Antiviral Drug Candidate Myrcludex B and the Nucleotide Analogue Reverse Transcriptase Inhibitor Tenofovir *[completed]*

- Study MYR201 (Part I): A Phase 1b/2a Randomized, Open-label Clinical Trial of Daily Bulevirtide Versus Entecavir in Patients with HBeAg Negative Chronic Hepatitis B (Russia) *[completed]*

- Study MYR201 (Part II): Randomized Open-label Substudy of Daily Bulevirtide Plus Pegylated Interferon-alpha-2a in Patients with HBeAg Negative Chronic Hepatitis B Co-infected With Hepatitis Delta (Russia) [completed]

- Study MYR202: A 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 (Germany, Russia) *[completed]*

- Study MYR203: A Multicenter, Open-label, Randomized, Comparative, Parallel-group Phase 2 Study to Assess the Efficacy and Safety of the Combination of Bulevirtide and Pegylated Interferon-alpha-2a as Compared With Pegylated Interferon-alpha-2a Monotherapy in Patients With Chronic Hepatitis B With Delta-agent (Russia) *[completed]*

- Study MYR204: A Multicenter, Open-label, Randomized Phase 2b Clinical Study to Assess Efficacy and Safety of Bulevirtide in Combination with Pegylated Interferon alfa-2a in Patients with Chronic Hepatitis Delta *[ongoing]*

- Study MYR301: A Multicenter, Open-label, Randomized Phase 3 Clinical Study to Assess Efficacy and Safety of Bulevirtide in Patients with Chronic Hepatitis Delta [*ongoing*]

MYR101 Study

A Phase 1 single-dose study (MYR101) was conducted in 36 healthy male patients. Selected dose groups were 0.3 µg, 3 µg, 10 µg, 100 µg, 800 µg, 3 mg, 5 mg, 10 mg, and 20 mg for intravenous application and subcutaneous administration was carried out with 800 µg, 5 mg, and 10 mg. Each dose was administered to a cohort of 3 consecutive patients. For all cohorts and both administration routes, administration of bulevirtide was uneventful and well tolerated. After administration, there were no relevant changes in vital signs (blood pressure, heart rate, respiratory rate, and body temperature), 12-lead electrocardiograms (ECGs), and safety laboratory values. Overall, 85 adverse events (AEs) were observed in 29 individuals, none of these was serious. Events were equally distributed between cohorts and no organ system was predominantly affected. Seventy-four events were mild in nature, nine moderate, and only 2 were severe (Grade 3) according to Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 criteria (increased lipase; increased amylase). Anti-drug antibodies were measured until 6 months after exposure and were negative for all individuals.

Bulevirtide has been well tolerated in all patients, no serious adverse event (SAE) and no dose limiting toxicities occurred. The AEs were mostly mild in nature and self-limiting and no pattern suggesting a relationship with bulevirtide or unexpected off-target effects were seen. There was no dose-dependency of AE frequency or severity. This matches the observations from animal studies, where bulevirtide exhibited a highly specific and exclusive binding to hepatocyte. Therefore, bulevirtide had a good safety profile even in the cohorts with high doses in this trial.

Bulevirtide showed strong dose-dependent pharmacokinetics; the area-under-the-time-plasma concentration curve increased disproportionally while the clearance and volume of distribution decreased with higher doses. The bioavailability of the drug after subcutaneous administration was estimated to be 88%. The release after subcutaneous administration was best described by a parallel slow and fast first-order process, where 59% of the bioavailable dose was absorbed fast and the remaining 41% of the dose was absorbed slowly with absorption half-lives of 1.3 h and 5.4 h, respectively. A simulation of the impact of various doses of bulevirtide on the occupancy of the binding target revealed that at doses of 10 mg most of the binding target was occupied > 80% for at least twenty hours in a simulated steady-state after subcutaneous administration.

MYR102 Study

A Phase 1 drug-interaction study (MYR102) in healthy patients investigated the influence of receptor-saturating dose on pharmacokinetics of anti-HBV drug tenofovir disoproxil fumarate (TDF). Twelve healthy patients received 245 mg of oral TDF for 5 days alone followed by 6 days of co-administration of 10 mg subcutaneous bulevirtide. Plasma samples were collected and bulevirtide, tenofovir, and plasma bile salts were quantified. Repeatedly, a 30 µg midazolam microdose was administered to determine the impact of the antivirals on cytochrome P450 enzyme (CYP)3A activity.

The combination of bulevirtide and tenofovir was well tolerated. A total of 28 AEs occurred in 10 out of 12 participants, 12 of which were considered to be at least possibly related to tenofovir or bulevirtide treatment (anemia [2], first-degree atrioventricular block [1], diarrhea [1], nausea [1], injection site hypersensitivity [2], increased alanine aminotransferase (ALT) [5], increased amylase [1], increased AST [1], increased lipase [2], muscular weakness [1], and headache [1]). With the exception of one Grade 3 increase in lipase levels, all treatment-related AEs were mild. Lipase levels showed marked day to day fluctuations in this participant. Two patients experienced localized hypersensitivity reactions for about 30 min after each administration of bulevirtide (erythema, pruritus) without accompanying signs of systemic anaphylaxis.

Bulevirtide did not have a significant effect on tenofovir plasma pharmacokinetics and renal clearance with TDF administration. Bulevirtide pharmacokinetic parameters after first and repeated dosing were comparable to those observed in two other clinical studies with the substance. Therefore, a clinically relevant influence of TDF on bulevirtide concentrations seems unlikely. Estimated metabolic clearance of midazolam exhibited a downward trend with a gradual decrease during the course of the study. Geometric mean values were 1022 mL/min (95% CI: 801.5, 1303) without co-medication, 869.1 mL/min (679.8, 1111) under TDF, and 724.8 mL/min (592.5, 886.7; p-value 0.02 vs baseline) under TDF and bulevirtide treatment.

Differences were significant between baseline and co-administration of TDF and bulevirtide, but not between TDF monotherapy (baseline immediately before start of bulevirtide) and combination therapy. Therefore, our results did neither confirm nor rule out an influence of bulevirtide on CYP3A activity. The small and clinically irrelevant inhibition of CYP3A activity by TDF or its prodrug might account for the statistically inconclusive results. Co-administration of regular TDF doses with bulevirtide was well tolerated and revealed no clinically relevant change in either drug's pharmacokinetics or CYP3A activity, suggesting that these drugs can be safely combined without dose modification.

CCI

[redacted]

CCI [redacted]

MYR201 Study (Part II – Chronic Hepatitis Delta)

This was a randomized, open-label, single-center, active-controlled, parallel-group study. Patients of both sexes at the age of 18 to 65 years with HBV/HDV co-infection confirmed by the presence of HBsAg for at least 6 months and positive anti-HDV antibodies status for at least 3 months before screening, as well as positive results for HDV RNA within the screening period were enrolled in the study. A total of 24 patients were randomized in 1:1:1 ratio into the 3 treatment arms:

Arm A (n=8): Bulevirtide 2 mg daily SC injection for 24 weeks, followed by pegylated interferon alph-2a for 48 weeks + 24 weeks follow-up

Arm B (n=8): Bulevirtide 2 mg daily SC and pegylated interferon alpha-2a for 24 weeks, followed by monotherapy with pegylated interferon alpha-2a for 24 weeks + 24 weeks follow-up

Arm C (n=8): pegylated interferon alpha-2a for 48 weeks + 24 weeks follow-up

Safety and tolerability, CCI [redacted] and virological responses were assessed in this trial. Levels of HBsAg, HBV DNA, HDV RNA, and ALT were used to assess efficacy.

The 24-week therapy with bulevirtide both in Arm A and Arm B was not associated with higher number of HBsAg responders (defined as HBsAg decline of ≥ 0.5 $\log_{10}$ IU/mL) as compared with Arm C.

Combination therapy with bulevirtide 2 mg and pegylated interferon alpha-2a for 24 weeks showed the highest rate of fast HBV DNA responders (defined as HBV DNA decline by > 1 $\log_{10}$ IU/mL; 6/8 patients). Overall, both bulevirtide-containing regimens (Arm A and B) showed more considerable HBV DNA response as compared with pegylated interferon alpha-2a monotherapy (Arm C). At Week 48, there were 5/8 responders in Arm A, 4/8 in Arm B and 3/8 in Arm C. At Week 72 there were 5/8 responders in Arm B. At the end of follow-up, the number of responders decreased in all treatment groups: there were 3/8 responders in Arm A, 3/8 responders in Arm B and 2/8 responders in Arm C (Full Analysis Set [FAS]).

All treatment regimens demonstrated a considerable number of HDV RNA responders (defined as HDV RNA decline by > 1 $\log_{10}$ IU/mL) at Week 24. Monotherapy with bulevirtide showed response rates comparable to response rates observed in patients treated with pegylated interferon alpha-2a (6/7 patients). The combination treatment of bulevirtide + pegylated interferon alpha-2a demonstrated the highest response rate, thus indicating a potential synergistic

effect (7/8 patients). HDV RNA became undetectable in 2 of 7 patients treated with bulevirtide (Arm A) and pegylated interferon alpha-2a (Arm C) and in 5 of 8 patients treated with bulevirtide + pegylated interferon alpha-2a (Arm B). Further during the treatment there was an obvious decrease in the number of responders after the cessation of bulevirtide in Arm A and Arm B, while no changes were observed in Arm C.

The highest rate of ALT responders was observed after the 24-week monotherapy with bulevirtide (Arm A); however further switching to pegylated interferon alpha-2a led to the decrease of ALT response. No considerable difference was observed between Arm B and Arm C.

All randomized patients (24/24, 100.0%) experienced at least 1 AE during the study. A total of 226 AEs were reported: 85 AEs in Arm A, 59 AEs in Arm B and 82 AEs in Arm C. The AEs were predominantly clustered in the same 3 SOCs: 'Blood and lymphatic system disorders', 'Investigations', 'General disorders and administration site condition'. The preferred terms (PTs) with the most AEs reported were leucopenia, neutropenia, thrombocytopenia, each reported in more than 5 patients from each treatment group. The most common biochemical abnormalities were AST and ALT increased with the higher incidence observed in Arm A (6 and more patients) as compared with Arm B and C (3 patients). Influenza-like illness was the most reported AE within the SOC "General disorders and administration site conditions".

The majority of AEs were of mild or moderate in intensity. A few patients experienced severe AEs during the study: 1 patient in Arm B and 2 patients in each Arm A and Arm C. Severe AEs were hematological (leucopenia, neutropenia, thrombocytopenia) and biochemical (ALT, AST, GGT increased) abnormalities.

There was a 100% incidence (8/8 patients) of the pegylated interferon alpha-2a-related AEs in each treatment group, while the incidence of the bulevirtide-related AEs comprised 37.5% (3 patients) in Arm A and 12.5% (1 patient) in Arm B. Those related to pegylated interferon alpha-2a were leucopenia, neutropenia, thrombocytopenia, anemia, ALT, AST, GGT, bilirubin increased, aPTT prolonged, influenza-like illness, fatigue, pyrexia, dizziness, irritability and rash. The bulevirtide-related AEs included single cases of hematological disorders (leucopenia, neutropenia, thrombocytopenia and eosinophilia).

There were no deaths or other SAEs during the study. One patient discontinued the study due to AE: patient from Arm B who experienced rash of moderate intensity that was judged to be related to pegylated interferon alpha-2a.

CCI [redacted]

MYR202 Study (Completed)

MYR202 study evaluated the efficacy and safety of bulevirtide at daily doses of 2, 5, or 10 mg in combination with TDF compared with TDF alone in patients with chronic hepatitis D.

The primary efficacy endpoint was HDV RNA response at Week 24 was defined as undetectable HDV RNA or a decrease by ≥ 2 $\log_{10}$ IU/mL from baseline. Combined response was defined as fulfilment of two conditions simultaneously: undetectable HDV RNA or decrease by ≥ 2 $\log_{10}$ IU/mL from baseline; ALT normalization. The percentage of patients with HDV RNA response and combined response at Week 24 is shown in Table 2. There was significantly higher percentage of patients with HDV RNA response at Week 24 in all bulevirtide groups compared to TDF group ($p < 0.0001$ for all bulevirtide groups).

Table 2. Patients With HDV RNA Response and Combined Response at Week 24 (MYR202 Study, Modified Intention-to-Treat Population)

	Bulevirtide 2 mg + TDF (N=28)	Bulevirtide 5 mg + TDF (N=32)	Bulevirtide 10 mg + TDF (N=30)	TDF (N=28)
Patients with HDV RNA response at Week 24, n (%)	15 (53.6)*	15 (46.9)*	24 (80.0)*	1 (3.6)
Patients with combined HDV RNA/ALT response at Week 24, n (%)	6 (21.4)	8 (25.0)**	11 (36.7)***	0

* p<0.0001 compared to TDF (Wald test for superiority by margin of 5%)
** p<0.05 compared to TDF (Fisher's exact test)
*** p<0.001 compared to TDF (Fisher's exact test)
Reference: MYR202 Interim Clinical Study Report [32]

MYR203 Study (Completed)

MYR203 aimed to evaluate the efficacy and safety of bulevirtide at daily doses of 2, 5, or 10 mg in combination with pegylated interferon, bulevirtide at daily dose of 2 mg, and bulevirtide at daily dose of 5 mg twice daily in combination with TDF compared with pegylated interferon alone in participants with CHD.

A total of 90 participants were randomized into 6 treatment groups, each of 15 participants:

Group A: pegylated interferon 180 µg

Group B: bulevirtide 2 mg + pegylated interferon 180 µg

Group C: bulevirtide 5 mg + pegylated interferon 180 µg

Group D: bulevirtide 2 mg

Group E: bulevirtide 10 mg (10 mg once a day) + pegylated interferon 180 µg

Group F: bulevirtide 10 mg (5 mg twice daily) + TDF

The primary efficacy endpoint was defined as the proportion of participants with a negative polymerase chain reaction (PCR) result of HDV RNA (HDV RNA negativation) at Week 72 (end of the follow-up period).

At Week 72, the primary efficacy endpoint was achieved by 8/15 (53.3%; 95% CI: 26.6-78.7%), 5/15 (33.3%; 95% CI: 11.8 61.6%), and 4/15 (26.7%; 95% CI: 7.8-55.1%) of the participants treated with bulevirtide 2 mg + pegylated interferon (Group B), bulevirtide 5 mg twice daily + TDF (Group F) and bulevirtide 5 mg + pegylated interferon (Group C), respectively.
One participant from each of the other bulevirtide groups, Group D and Group E, achieved the primary endpoint (1/15 [6.7%; 95% CI: 0.2 31.9%]). No participant (0/15 participants) treated with pegylated interferon only (Group A) achieved the respective HDV RNA response.

MYR301 Study (Ongoing)

MYR301 is an ongoing study that is comparing the efficacy and safety of bulevirtide administered as delayed treatment (followed by 10 mg/day after 48 weeks) versus immediate treatment (2 mg or 10 mg/day) 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 the treatment period, which is 144 weeks:

- Treatment Group A: Delayed treatment with bulevirtide 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 bulevirtide 2 mg/day for 144 weeks with a further follow-up period of 96 weeks
- Treatment Group C: Immediate treatment with bulevirtide 10 mg/day for 144 weeks with a further follow-up period of 96 weeks

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

The primary efficacy endpoint was the proportion of participants achieving combined response at Week 48. Combined response was defined as fulfilment of 2 conditions simultaneously:

- Undetectable (< limit of detection [LoD]) HDV RNA or decreased by ≥ 2 $\log_{10}$ IU/mL from baseline
- ALT normalization

At Week 48, there was a clear treatment effect for participants receiving bulevirtide 2 mg or bulevirtide 10 mg when compared with participants in the delayed treatment group. The proportion of participants who achieved combined response in the active treatment groups was as follows:

- Bulevirtide 2 mg treatment group: 44.9% (95% CI: 30.7% to 59.8%); $p < 0.0001$ when compared with delayed treatment (2.0% [95% CI: 0.0% to 10.4%])
- Bulevirtide 10 mg treatment group: 48.0% (95% CI: 33.7% to 62.6%); $p < 0.0001$ when compared with delayed treatment (2.0% [95% CI: 0.0% to 10.4%])

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

- Bulevirtide 2 mg treatment group versus delayed treatment group: 42.9% (96% CI: 27.0% to 58.5%; $p < 0.0001$)

- Bulevirtide 10 mg treatment group versus delayed treatment group: 46.0% (96% CI: 30.5 to 61.4%; $p < 0.0001$)

Bulevirtide was generally well tolerated by participants with CHD. There were no deaths, SAEs related to study drug, SAEs reported for > 1 participant in any of the treatment groups, or AEs that led to premature discontinuation of study drug. Common AEs were generally consistent with those expected in the participant population and the known safety profile of the study drug. Injection site reactions were very commonly observed in participants treated with bulevirtide, with incidences of 16.3% and 30.0% observed in the 2 mg and 10 mg treatment groups, respectively.

Most hepatic laboratory abnormalities were Grade 1 or 2; there were 2 participants who had Grade 3 or 4 hepatic abnormalities. There does not appear to be an association between the development of pruritus and elevated bile salt levels with bulevirtide, given that similar changes in bile salt levels were seen in those participants with or without these AEs.

MYR204 Study (Ongoing)

MYR204 is an ongoing that is comparing the efficacy and safety of bulevirtide (2 and 10 mg) + pegylated interferon alpha with bulevirtide monotherapy (10 mg per day) and pegylated interferon alpha monotherapy in participants with CHD. Participants were randomized in a 1:2:2:2 ratio to 1 of the following 4 treatment groups for the treatment period, which is 96 weeks:

- Group A (n = 25): pegylated interferon alpha 180 µg once weekly SC for 48 weeks, with an additional 48 weeks of follow-up

- Group B (n = 50): Bulevirtide 2 mg once daily SC in combination with pegylated interferon alpha 180 µg once weekly SC for 48 weeks followed by bulevirtide 2 mg once daily SC for 48 weeks and an additional 48 weeks of follow-up

- Group C (n = 50): Bulevirtide 10 mg once daily SC in combination with pegylated interferon alpha 180 µg once weekly SC for 48 weeks followed by bulevirtide 10 mg once daily SC for 48 weeks and an additional 48 weeks of follow-up

- Group D (n = 50): Bulevirtide 10 mg once daily SC for 96 weeks, with an additional 48 weeks of follow-up

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

The primary efficacy endpoint is the sustained virological response 24 (SVR 24) defined as undetectable HDV RNA (HDV RNA < LoD) at 24 weeks after the scheduled end of treatment (study Week 120 for Arm B, Arm C, and Arm D).

The secondary efficacy endpoints are as follows:

- Undetectable HDV RNA at Week 48 (all arms) or Week 96 (Arm B, Arm C, and Arm D)
- Combined sustained response at Week 24 and Week 48 after the scheduled end of treatment, where combined response is defined as fulfilment of 2 conditions simultaneously:
  - Undetectable HDV RNA or decrease by ≥ 2 $\log_{10}$ IU/mL from baseline
  - ALT normalization, defined as an ALT value within the normal range, based on the central laboratories [Russian sites: ≤ 31 U/L for females and ≤ 41 U/L for males; all other sites: ≤ 34 U/L for females and ≤ 49 U/L for males])
- Sustained virological response 48 (SVR 48) defined as undetectable HDV RNA at Week 48 after the scheduled end of treatment
- Change from baseline in liver stiffness as measured by elastography at Week 48, Week 96, and Week 144

Both the primary and secondary efficacy endpoints have not been reached and thus not presented herein.

Treatment with bulevirtide monotherapy and in combination with pegylated interferon alpha was generally safe and well tolerated. The majority of AEs which occurred in the combination arms, where 2 mg or 10 mg of bulevirtide was administered with pegylated interferon alpha, are consistent with the known toxicity profile of pegylated interferon alpha, whereas no trends for augmentation of pegylated interferon alpha associated toxicities by bulevirtide were evident. Refer to the bulevirtide investigator's brochure for details on nonclinical and clinical studies.

1.4. Study Rationale

Currently, information about efficacy and safety of bulevirtide in participants with CHD is available for 24-week treatment (MYR202 study). This study is designed to assess the long-term efficacy and safety of bulevirtide in patients with CHD. Primary efficacy and safety data will be assessed at Week 48, when bulevirtide at 2 and 10 mg daily doses will be compared with delayed treatment. After Week 48, patients of delayed treatment group in this study will be switched to bulevirtide at 10 mg daily dose for additional 96 weeks. The total duration of treatment period in this Phase 3 study will be 144 weeks.

The period of 48 weeks of no treatment in this Phase 3 study is justified by the absence of any approved therapy or an effective treatment regime for the respective indication; furthermore, patients of the delayed treatment arm shall receive a 96-week treatment of the 10 mg bulevirtide after the assessment of the primary endpoint.

After the analysis of the primary endpoint, the treatment will be continued for the period of up to 3 years to investigate the optimal therapy duration. During the treatment free follow-up period, the possibility of the sustained virologic response shall be assessed. Whereas the study is not powered to investigate the difference in clinical outcomes such as death, cirrhosis decompensation or liver transplantation, those endpoints will be captured, and the information will be used in the overall concept of the clinical confirmation.

1.4.1. Rationale for Patient Population

In patients with HDV infection, therapeutic options are very limited or absent, as no drug is approved for treatment of this condition. In previous clinical trials administration of bulevirtide in subjects with HDV infection resulted in a decrease in HDV RNA and ALT values (see Section 1.3.2).

To ensure balance between groups, stratification by the presence of liver cirrhosis will be employed. Patients should receive nucleoside/nucleotide analogues at screening, treatment and/or follow-up period if required for control of the underlying chronic HBV infection, if indicated by the current clinical practice guidelines (EASL and AASLD). Inclusion of the described population is considered to be ethically appropriate and justified by data obtained in the previous study.

Patients with ALT $\geq 10 \times$ ULN, creatinine clearance < 60 mL/min, total bilirubin ≥ 34.2 µmol/L, hepatitis C virus (HCV), HCC, other significant or unstable disease will not be allowed to enter the study.

1.4.2. Rationale for Selection of the Dose of the Study Drug

Bulevirtide dose of 10 mg/day SC was selected as HDV RNA response and combined HDV RNA/ALT response rate at Week 24 in MYR202 Phase 2 study were numerically higher in the respective patients compared with patients who received other doses of bulevirtide in MYR202 study (see Section 1.3.2).

Bulevirtide dose of 2 mg/day SC will be investigated as it was shown to be active and has demonstrated excellent safety profile. Compared with the 5 and 10 mg bulevirtide doses, the 2 mg bulevirtide dose has been shown to be associated with still notable efficacy and to be safe and well tolerated. Specifically, the 2 mg dose had a lower virological effect compared with the 10 mg dose, but the response was still very significant. The effects of both doses on ALT normalization were similar, whereas the effect on bile salts increase was less pronounced with 2 mg dose.

1.5. Benefit/Risk Assessment

Bulevirtide has undergone extensive nonclinical testing. Detailed information on potential risks associated with NTCP inhibition is provided in the risk-benefit section of the "investigator's brochure". Several clinical studies evaluating pharmacokinetics, CCI [redacted] safety and efficacy of bulevirtide have been completed (see Section 1.3.2). An important risk identified in clinical trials was hepatitis exacerbation after bulevirtide cessation. Monitoring of ALT levels, liver function, HDV RNA, HBV DNA is recommended after the end of the study or the event of

early study termination. The available clinical data supports a clinical benefit in the proposed target population given the demonstrated favorable effects of bulevirtide in terms of HDV RNA decline, ALT normalization, and liver stiffness amelioration.

The design of this study contains adequate measures to mitigate risk factors and adequate safety monitoring to protect the subjects. In the context of the progressive, severe, and debilitating nature of CHD, the balance between risks that have been identified from cumulative safety data for bulevirtide and anticipated efficacy/benefits remains favorable.

The sponsor realizes that extraordinary measures may need to be implemented and trials management may need to be adjusted due to unexpected risks which may increase due to external unavoidable circumstances, including COVID-19 pandemic spread in the world, eg, for subjects safety, trial participants being in self-isolation/quarantine, limited access to public places (including hospitals) due to the risk of spreading infections, and health care professionals being committed to critical tasks.

Clinical trial nosology is CHD, which is a life-threatening disease with no currently approved therapeutic options. As the overall well-being and best interests of the participant should be considered, in trials for patients with life-threatening or severely debilitating conditions, in general it is of the best interest for the participants to remain receiving the trial treatment. Unplanned interruption of the bulevirtide treatment may lead to negative medical consequences including hepatitis flairs. The treatment interruption should be avoided and each case of interruption, where it is inevitably, should be closely monitored for safety of the subjects.

The investigators, in coordination with the sponsor, should assess the risks of any changes considered in the trial for each single patient and each single procedure with regard to the safety of the subject and the integrity of the trial data, with priority given to the safety of the subject. The safety of the participant is of primary importance and risks of participation in the trial, in particular with added challenges due to COVID-19, should be weighed against anticipated benefit for the participant and society.

2. STUDY OBJECTIVES

2.1. Objectives

Primary Objective:

The primary objective of this study is to evaluate the efficacy of bulevirtide administered subcutaneously for 48 weeks at a dose of 2 mg or 10 mg once daily for treatment of CHD in comparison to delayed treatment.

Secondary Objectives:

- To evaluate optimal treatment duration
- To assess the safety of bulevirtide

CCI [redacted]

2.2. Endpoints

Primary Efficacy Endpoint:

Combined response at Week 48. Combined response is defined as fulfilment of two conditions simultaneously:

- Undetectable (< LoD) HDV RNA or decrease by ≥ 2 $\log_{10}$ IU/mL from baseline;
- ALT normalization.

Secondary Efficacy Endpoints:

- Undetectable HDV RNA at Week 48
- ALT normalization at Week 48
- Undetectable HDV RNA 24 weeks after scheduled end of treatment (SVR24)
- Undetectable HDV RNA 48 weeks after scheduled end of treatment (SVR48)
- Change from baseline in liver stiffness as measured by elastography at Weeks 48, 96, 144, 192, and 240

CCI

Safety Endpoints:

- Frequency and nature of AEs (based on assessments of clinical events, physical examination, vital signs, ECG, and laboratory tests)
- Changes in vital signs
- Changes in PR, 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)

CCI [redacted]

Pharmacokinetic Variables:

- Plasma concentration of bulevirtide

Other Variables:

- NTCP polymorphism
- HBeAg and HBeAg antibodies status at all postbaseline assessments (for patients with positive HBeAg at screening)
- 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; semi-quantitative analysis of HBsAg and HDAg with immunohistochemistry)

3. OVERALL STUDY DESIGN

This is a randomized, open-label, parallel-group, multicenter Phase 3 study that will evaluate the efficacy and safety of bulevirtide in subjects with CHD who have no adequate treatment options.

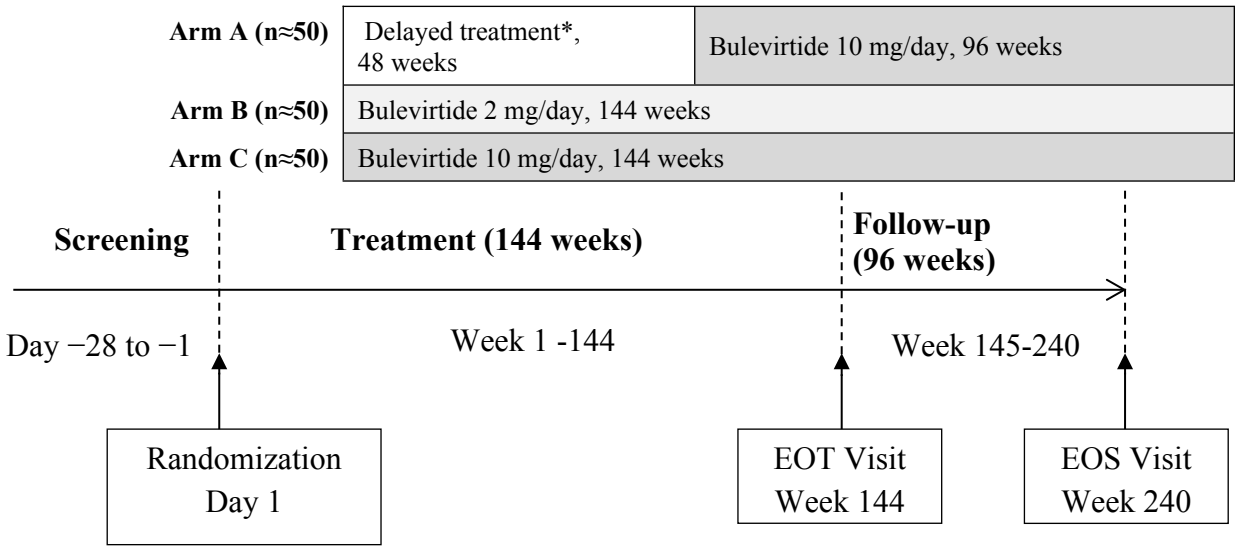
This study will be conducted at approximately 24 sites across approximately 6 countries globally which may include Germany, Russia, Italy, Georgia, US, and Sweden. A total of 150 subjects will be randomized.

Subjects will be assessed for eligibility to enter the study during a 4-week Screening period. Eligible subjects will be randomized at Visit 1 in a 1:1:1 ratio with stratification for the presence of liver cirrhosis (no/yes) to receive delayed treatment with bulevirtide 10 mg/day after an observational period of 48 weeks (Arm A), immediate treatment with bulevirtide 2 mg/day (Arm B) or immediate treatment with bulevirtide 10 mg/day (Arm C) for 144 weeks.

At Week 48 subjects from delayed treatment group (Arm A) for CHD will be switched to bulevirtide 10 mg/day for 96 weeks. The total duration of treatment period is 144 weeks. After completion of the treatment period, subjects will be followed for additional 96 weeks. For all subjects the total amount of time to complete the study will be 240-244 weeks (inclusive of the Screening, Treatment, and Follow-Up Periods).

The study will be considered to have started when the first patient has provided signed informed consent, and will be considered to have finished after the last patient has completed the last follow-up visit. A scheme of the study design is presented in Figure 1. The schedule of events to be conducted during the 144-week Treatment Period and the safety Follow-Up Period is presented in Table 1. Treatment and all study procedures will be performed on an outpatient basis (except for hospitalization for biopsy procedure, if required).

Figure 1. Study Plan



EOT = end of treatment; EOS = end of study; HDV = hepatitis delta virus
*Delayed treatment means no treatment for HDV infection for 48 weeks.

3.1. Randomization

Patients eligible for the study are randomized after completion of all procedures scheduled for Screening and Day 1 (except study drug administration, Patient Diary dispensing, sample collection for pharmacokinetics and assessment of AEs; see Table 1) and confirmation of participant's eligibility (See Section 4).

Patients eligible for the study will be allocated into the treatment group through an electronic randomization system. Electronic randomization system must be accessed as close to the initiation of study treatment as possible to avoid randomization of patients who ultimately decide not to participate in the trial.

A manual will be provided to investigator with instructions detailing how to work with electronic randomization system. Investigators must be trained to use electronic randomization system before randomization.

Randomization will be performed with 1:1:1 allocation ratio with stratification for the presence of liver cirrhosis (no/yes); each patient will be assigned a unique randomization code.

3.2. Blinding

This is an open-label study. Central laboratories (except the laboratories for pharmacokinetics, CCI [redacted] NTCP polymorphism, and Resistance tests) will be blinded to actual treatment allocation.

4. SELECTION OF STUDY POPULATION

This is an international study and it is expected that subjects will be enrolled at approximately 24 study sites across approximately 6 countries. A total of 150 subjects will be randomized. Enrolment will stop as soon as the target number of randomized subjects is reached.

Before randomization of study subject eligibility must be confirmed by the medical monitor. Investigator should record all relevant information about the study subject in electronic case report form (eCRF) (all forms with information related to assessment of eligibility) and provide blinded copy of medical record confirming positive serum HDV antibody results or PCR results for serum/plasma HDV RNA for at least 6 months before Screening and other relevant medical information if required to confirm subject's eligibility.

The laboratory results from Day 1 are not supposed to be used for patient's eligibility assessment.

All inclusion and exclusion criteria should be confirmed according to Appendix 1 to the Protocol.

4.1. Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1) Provision of signed and dated informed consent form (ICF).

2) Male or female, aged 18-65 years (inclusive).

3) Positive serum anti-HDV antibody results or PCR results for serum/plasma HDV RNA for at least 6 months before Screening.

4) Positive PCR results for serum/plasma HDV RNA at Screening.

5) ALT level > 1 × ULN, but less than 10 × ULN.

6) Serum albumin > 28 g/L.

7) Negative urine pregnancy test for females of childbearing potential.

8) Inclusion criteria for female subjects:

   - Postmenopausal for at least 2 years, or
   - Surgically sterile (total hysterectomy or bilateral oophorectomy, bilateral tubal ligation, staples, or another type of sterilization), or
   - Abstinence from heterosexual intercourse throughout the study, or

- Willingness to use highly effective contraception (double barrier method or barrier contraception in combination with hormonal or intrauterine contraceptive) throughout the study and for 3 months after the last dose of the study medication for patients discontinued during the treatment period.

9) Male subjects must agree to use a highly effective contraception (double barrier method or barrier contraception in combination with hormonal or intrauterine contraceptive used by female partners) and not to donate sperm throughout the study and for 3 months after the last dose of the study medication for patients discontinued during the treatment period.

4.2. Exclusion Criteria

An individual who meets any of the following criteria cannot take part in this study:

1) Child-Pugh hepatic insufficiency score over 7 points. Uncomplicated oesophageal varices allowed; Subjects with current bleeding or ligation, or history of bleeding or ligation within the last 2 years are excluded.

2) HCV or uncontrolled HIV co-infection. Subjects with HCV antibodies can be enrolled, if screening HCV RNA test is negative. Subjects with HIV infection can be enrolled if CD4+ cell counts are > 500/mL and HIV RNA is below LoD for at least 12 months.

3) Creatinine clearance < 60 mL/min as estimated using Cockcroft-Gault formula.

4) Total bilirubin ≥ 34.2 μmol/L. Patients with higher total bilirubin values may be included after the consultation with the study medical monitor, if such elevation can be clearly attributed to Gilbert's syndrome associated with low-grade hyperbilirubinemia.]

5) Evidence of an active or suspected malignancy or a history of malignancy, or an untreated pre-malignancy disorder within the last 5 years (with the exception of successfully treated carcinoma of the cervix in situ and successfully treated basal cell carcinoma and squamous cell carcinoma not less than 1 year prior to screening [and no more than 3 excised skin cancer within the last 5 years prior to screening]) or history of hepatic carcinoma.

6) Systemic connective tissue disorders.

7) New York Heart Association (NYHA) Class III-IV congestive heart failure.

8) Patients with uncontrolled arterial hypertension: systolic blood pressure > 150 mm Hg and/or diastolic blood pressure > 100 mm Hg at Screening.

9) Previous or unstable concurrent diseases or conditions that prevent subject's enrolment into the study.

10) Patients with mental disorders or social circumstances that preclude them from following protocol requirements.

11) Current or previous (within last 2 years) decompensated liver disease, including coagulopathy, hepatic encephalopathy and esophageal varices hemorrhage.

12) One or more additional known primary or secondary causes of liver disease, other than hepatitis B (eg, alcoholism, autoimmune hepatitis, malignancy with hepatic involvement, hemochromatosis, alpha-1 antitrypsin deficiency, Wilson's Disease, other congenital or metabolic conditions affecting the liver, congestive heart failure or other severe cardiopulmonary disease, etc). Gilbert's syndrome, a benign disorder associated with low-grade hyperbilirubinemia, will not exclude patients from participation in this trial. Autoimmune hepatitis stigmata attributed to HDV infection in the opinion of the investigator are allowed.

13) White blood cells (WBC) count < 3000 cells/mm^3 (< 1500 if African patients).

14) Neutrophil count < 1500 cells/mm^3 (< 1000 if African patients).

15) Platelet count < 60,000 cells/mm^3.

16) Use of prohibited psychotropic agents at Screening.

17) Use of interferons within 6 months before Screening.

18) History of solid organ transplantation.

19) Current alcohol abuse or alcohol abuse within 6 months prior to enrolment in this study; past or current drug addict.

20) History of disease requiring regular use of systemic glucocorticosteroids (inhalative glucocorticosteroids are allowed) or other immunosuppressants.

21) Pregnant or breast-feeding females.

22) Participation in another clinical study with investigational drugs within 30 days prior to randomization.

23) Receipt of bulevirtide previously, eg, in clinical trials.

24) Inability to follow protocol requirements and undergo all protocol procedures. NOTE: Patients with medical contraindication for liver biopsy are allowed to participate in this study. Such patients will exempt from liver biopsy requirements in this study.
Patients receiving prohibited treatment at Screening cannot be included into the study unless this treatment is withdrawn prior to randomization.

4.3. Withdrawal Criteria

Participants are free to withdraw from participation in the study at any time upon request. However, investigator will make every reasonable effort to document exact reasons for subject's decision to withdraw and enter them into eCRF.

Subjects may be withdrawn from the study in the following circumstances:

1) Informed consent withdrawal by the subject.

2) Investigator believes that it is not in the subject's best interests to continue participation in the study.

3) Investigator decides to withdraw the study subject due to a serious protocol deviation/violation.

4) Concurrent disease or progression of the underlying disease that, in the opinion of investigator, can significantly affect evaluation of subject's clinical status.

5) In case of suspected pancreatitis, the treatment with the study medication should be stopped and further diagnostic procedures undertaken.

6) Use of prohibited medication is required.

7) Unacceptable toxicities, or a reaction that, in the investigator's opinion, precludes further study procedures or requires discontinuation of the subject from the study.

8) Pregnancy during the study.

9) Subject is lost to follow-up.

Investigator is responsible for obtaining and documenting the reason(s) for subject's withdrawal from the study after randomization and entering all relevant information into eCRF, including detailed information about the reason for the subject's withdrawal from the study when subjects agrees to provide such information. If the subject was withdrawn due to an AE, the primary term or a laboratory test must be reported in the eCRF, and investigator must make every effort to accurately report all AE characteristics.

Investigator should report information about withdrawn subjects to the sponsor and the clinical research associate (CRA) within 24 hours.

4.4. Replacement of Participants

Study subjects will not be replaced.

4.5. Premature Termination of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to investigator and regulatory authorities. If the study is prematurely terminated or suspended, the principal investigator (PI) will promptly inform the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) and will provide the reason(s) for the termination or suspension; the PI will also promptly inform the study subjects and will assure appropriate therapy and follow-up.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

5. TREATMENTS

5.1. Treatments Administered

5.1.1. Bulevirtide

Brief description of study drug bulevirtide is presented below. Additional information can be found in investigator's brochure. The product will be supplied in sterile vials to be reconstituted in 1 mL water for injection prior to administration.

Drug Formulation: Lyophilized powder for injections.

Composition

Active Ingredient: Bulevirtide, 5.0 or 2.0 mg/vial.

Excipients: sodium carbonate, sodium hydrocarbonate, mannitol, hydrochloric acid, and sodium hydroxide are used for solution of the drug substance before aseptic filling and lyophilization. Pharmaceutically pure substances are used.

Physical Form: white to off-white powder.

Appearance of the Solution: clear and colorless.

Packaging

Container: 2R injection vial, colorless glass, European Pharmacopoeia Hydrolytic class I. Closure: Lyophilization rubber stopper for 2R vials, European Pharmacopoeia Type I (diameter 13 mm). Closure: 13 mm bordered cap, aluminum with plastic disc.

Single use vials.

Storage

At the central depot, during transportation and at study site, the drug should be stored at −20 ± 5 °C in the dark place with temperature monitoring.

At home, it is allowed for study subjects to store the drug at +2 °C to 8 °C (in the refrigerator).

Temporary storage of the drug at room temperature up to 25 °C for not more than three days is allowed.

In case of other deviations of the cold chain conditions such deviation should be promptly reported to the sponsor and the product should be placed to quarantine and should not be used prior to sponsor's authorization.

After reconstitution of vial contents with water for injection the drug remains stable for 120 minutes at room temperature.

5.2. Labelling of Bulevirtide

Labelling of packages of the study product, apart from the compulsory information (pharmaceutical form of the product, amount in the package, storage conditions and shelf life, manufacturer data, release date and batch number), will include the following note "For clinical studies", study protocol No., and other information as required by local regulations.

5.3. Dosing and Administration

5.3.1. Supplying Patients with Bulevirtide

Investigator or designated person is responsible for supplying patient with the study drug.

Patients randomized to receive bulevirtide at 2 mg daily dose are supplied with sufficient quantity of the study drug and materials assuming that for each day of the treatment period the following is needed:

- 1 vial with bulevirtide 2 mg,
- 1 vial with sterile water for injection (minimum 1 mL),
- 1 disposable syringe (with 2 needles),
- Alcohol pads for disinfection

Patients randomized to receive bulevirtide at 10 mg daily dose are supplied with sufficient quantity of the study drug assuming that for each day of the treatment with bulevirtide the following is needed:

- 2 vials with bulevirtide 5 mg,
- 2 vials with sterile water for injection (minimum 1 mL),
- 2 disposable syringes (with 2 needles each),
- Alcohol pads for disinfection

If, in the case of external unavoidable circumstances, including COVID-19 pandemic spread in the world, it is not possible for patient to visit the site for drug supplying, upon consent of the patients and by the decision of investigator, the drug may be delivered to the patient.

5.3.2. Administration of Bulevirtide

Bulevirtide is administered by study subjects at home and by the responsible person at site. Bulevirtide is administered at study sites on days of visits to study sites and at home for all other days. Patients should be instructed NOT to administer bulevirtide at home at days of visits to study sites. At these days bulevirtide is administered at study site in accordance with schedule of events for assessment of CCI and pharmacokinetics of the study drug (ie, sample for

CCI assessment is taken before administration of bulevirtide and sample for pharmacokinetics is taken 1h ± 15 min after bulevirtide dose).

Study site staff will instruct patients on procedures for storage, preparation and subcutaneous administration of bulevirtide. Instructions for patients will be provided within the Patient Diary.

Patients randomized to receive bulevirtide at 2 mg daily dose administer bulevirtide by 1 SC injection. Patients randomized to receive bulevirtide at 10 mg daily dose administer bulevirtide by 2 SC injections (5 mg of bulevirtide twice). For patients randomized to receive bulevirtide at 10 mg daily dose two injections are performed one after another without time lag between injections. Bulevirtide is administered daily.

Patient should schedule constant time for daily injection of study drug during the first week of treatment (given the time of visits to the study sites) and then should follow the estimated schedule of injection during all period of the study.

The interval between injections should be 24 ± 1 hours. The exact time for the next injection should be calculated from the previous injection with possible deviation of ±1 hour. Deviation of ±3 hours is allowed for days of visits to study sites.

To prepare study drug for injection content of each bulevirtide vial assigned for administration at current day is reconstituted with 1 mL of the supplied solvent and administered with the supplied syringe. Study drug should be reconstituted immediately before injection. Reconstituted solution is stable for 2 hours.

The injection sites are: the outer surface of the shoulder, anterolateral thigh surface or the anterolateral surface of the abdominal wall with developed subcutaneous fat. During the treatment period, injection sites may be changed.

5.4. Dose Adjustments/Modifications/Delays

General Aspects

If investigator believes that the patient requires temporary interruption in the bulevirtide treatment, he/she should discuss it with the study medical monitor.

In case the treatment is interrupted the investigator should maintain the patient's safety supervision, including the ALT monitoring.

Dose Adjustments

Dose adjustments are not allowed in this study.

Missed Dose

In case of a missed dose the following procedure is to be followed.

If a patient remembered of the missed dose before 4 hours have lapsed from the daily administration time frame, the dose should be administered. The next day, the planned dose should be administered at the initially set up time.

If more than 4 hours have passed from the planned time point, the dose should not be administered and should be considered missed, and the next day the planned dose should be administered at the initially set up time. The missed dose should be reported in a Patient Diary and eCRF.

Treatment Adherence

Patient Diary (see Section 6.7) will be in place to monitor dosing and adherence for each participant.

5.5. Accountability Procedures

Drug supplies should be stored in a secure area, accessed by authorized personnel only.

Drug inventory and accountability logs including details of the study drug received and dispensed to the patient, batch, and patient numbers must be kept.

5.6. Treatment Compliance

Both patient's diary information and drug accountability information will be used to estimate treatment compliance. Information about each study drug administration (ie, time of administration and administered dose) will be captured in patient's diary by patient. All empty vials of the study drug and unused drug are returned by patient to investigator at each visit. Patient's diary information and drug accountability information (ie, number of dispensed vials with the study drug and the number of returned empty vials of the study drug) is entered in eCRF at each visit of patient to study site.

5.7. Concomitant Therapy

All concomitant medications taken during study participation will be recorded on the eCRF. Medications to be reported in the eCRF are concomitant prescription medications, over-the-counter medications and non-prescription medications.

5.7.1. Treatment with Nucleoside/Nucleotide Analogues

Patients who are receiving the treatment with nucleoside/nucleotide analogue for chronic HBV infection will continue their treatment as prescribed at Screening and during the study participation.

For patients not receiving the treatment with nucleoside/nucleotide analogue for chronic HBV infection it should be initiated at Baseline visit or later in the study if indicated in accordance with the current EASL/AASLD treatment guidelines (33 and 34 are current as of November 2018). In particular, treatment should be started if one of following conditions is met:

- HBV DNA > 2,000 IU/mL, ALT > ULN and/or at least moderate liver necroinflammation or fibrosis
- Liver cirrhosis with any detectable HBV DNA level
- Patients with HBV DNA > 20,000 IU/mL and ALT > 2 × ULN should start treatment regardless of the degree of fibrosis
- Family history of cirrhosis or HCC
- Presence of extrahepatic manifestations

The sponsor will be providing tenofovir (tablets) if the drug cannot be made available for patients through routine medical care. In patients in whom tenofovir is contraindicated, entecavir (tablets) will be provided.

5.7.2. Prohibited Treatments

Treatment with the following drugs will not be permitted unless discussed with and approved by the study medical monitor.

- Systemic glucocorticosteroids (inhalative glucocorticosteroids are allowed)
- Immunomodulatory agents (drugs intended for treatment of common cold are allowed)
- Antiviral drugs for HBV and/or HDV treatment, apart from allowed nucleoside/nucleotide analogues
- Hematopoiesis-stimulating agents
- Sulfasalazine
- Ezetimibe
- Cyclosporine
- Substrates of organic anion transporting polypeptide (OATP)1B1: Atorvastatin, Bosentan, Docetaxel, Fexofenadine, Glecaprevir, Glyburide (glibenclamide), Grazoprevir, Nateglinide, Paclitaxel, Paritaprevir, Pitavastatin, Pravastatin, Repaglinide, Rosuvastatin, Simeprevir, Simvastatin (acid), Olmesartan, Telmisartan, Valsartan, Voxilaprevir [36, 37, 38, 39]
- Irbesartan
- Ritonavir

6. STUDY PROCEDURES

Schedule of study procedures is given in Table 1. Additional unscheduled visits and procedures may be performed in following cases:

- If additional procedures are considered by investigator to be necessary for monitoring patient's condition,
- In case of abnormal laboratory results,
- In case of sample sent to central laboratory was considered to be not analyzable,
- In case necessity to dispensing of additional study materials and/or study drug.

In case of early discontinuation of the study by study subject early discontinuation visit should be scheduled and performed. Procedures for early discontinuation visit are listed in Section 6.1.

6.1. Early Discontinuation Visit

Early discontinuation visit should be performed for subjects who discontinue the study prematurely. The visit should be scheduled and performed at the earliest convenience after the decision to discontinue patient from the study. Patients prematurely withdrawn during the treatment period should complete procedures of Visit 19/Week 144.

Patients prematurely withdrawn during the follow-up period should complete procedures of Visit FU 6/EOS.

6.2. Restrictions During the Study

Diet Restrictions

Subjects must attend study sites after fasting for at least 9 hours (water and concomitant medications are permitted) for the purpose of conducting the biochemistry.

Restrictions in Concomitant Treatment

Information is presented in Section 5.6

Contraception

Female Subjects

Women of childbearing potential must agree to use an adequate method of contraception throughout the study and for 3 months after the last dose of the study medication for patients discontinued during the treatment period.

Women of childbearing potential are females who have experienced menarche and do not meet the criteria of **Not** being of childbearing potential.

Women **Not** of childbearing potential are females who are postmenopausal or permanently sterilized (ie, bilateral tubal ligation greater than or equal to one menstrual cycle prior randomization, or have undergone a hysterectomy or bilateral oophorectomy). Postmenopausal is defined as 24 consecutive months with no menses without an alternative medical cause.

Adequate contraceptive precautions include one highly effective form of contraception or two effective forms of contraception.

The following contraception forms are considered highly effective:

- True abstinence when this is in line with the preferred and usual lifestyle of the patient. [Periodic abstinence (eg, calendar, ovulation, symptothermal post-ovulation methods) and withdrawal are not acceptable methods of contraception].

- Male partner is vasectomized (surgically sterilized). The vasectomized male partner should be the sole partner.

The following contraception forms are considered effective:

- Placement of intrauterine device or intrauterine system. Consideration should be given to the type of device being used, as there are higher failure rates quoted for certain types, eg, steel or copper wire.

- Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository.

- Hormonal contraceptive.

It should be noted that two forms of effective contraception are required. A double barrier method is acceptable which is defined as condom and occlusive cap (diaphragm or cervical/vault caps) if used together with spermicidal foam/gel/film/cream/suppository.

Should the female patient become sexually active while participating in the study, she must agree to use a double barrier method of contraception providing she is of childbearing potential.

Male Subjects

Male subjects who have female partner of childbearing potential must use an adequate method of contraception (as described above) and not to donate sperm throughout the study and for 3 months after the last dose of the study medication for patients discontinued during the treatment period.

The procedures to be followed if a female subject or female partner of a male subject becomes pregnant while enrolled in the study are described in Section 7.4.

6.3. Demographic and Other Baseline Characteristics

6.3.1. Demographics

The following demographic details as permitted by local regulations are to be collected during Screening:

- Date of birth
- Sex
- Race
- Smoking/alcohol/drugs abuse history and current use

6.3.2. Medical History

The following reporting periods should be followed:

- Information about diseases, conditions, and surgeries related to the liver is collected for a lifelong period,
- Information about other diseases, conditions, and surgeries is collected if they have occurred within 5 years before the Screening or regardless of the time if they are considered to be relevant by investigator.

The cirrhosis status including Child-Pugh Score (points) should be recorded in the source documents and eCRF for cirrhotic patients within the medical history collection at Screening.

6.3.3. Prior and Concomitant Therapy

All previous treatment for viral hepatitis should be recorded in the eCRF. Prior therapy for other diseases is collected for therapies that patient receives currently and therapies that were discontinued within 3 months before Screening.

Any medical treatment present at Screening or started after the first administration of study drug must also be entered in eCRF.

6.3.4. Weight, Height, Body Mass Index

Height will be recorded in meters (to the nearest cm) at Screening. Weight (kg) will be measured at Screening and during the study as indicated in the Schedule of Events (Table 1). Body mass index (BMI) at Screening will be calculated as follows: Body weight (kg)/[Height (m)]^2. All results should be recorded in the eCRF.

6.3.5. Pregnancy Test

Urine pregnancy test is required for women of childbearing potential (see Section 6.2). Pregnancy test will be done at Screening and during the study as indicated in the Schedule of Events (Table 1). Test strips will be used. The results will be documented in the eCRF.

6.3.6. Drug Screening

Urine test strips will be used to detect traces of methadone, benzodiazepines, cocaine, amphetamines, cannabinoids, opiates, barbiturates, tricyclic antidepressant. The list of prohibited drugs may vary based on country-specific regulations. The result will be documented in the eCRF.

6.3.7. Breath Alcohol Test

Alcohol levels in exhaled oxygen will be measured at Screening and Randomization/Baseline visit. Electronic breathalyzer will be used. The result will be documented in the eCRF.

6.3.8. Abdominal Ultrasound

Abdominal ultrasound will be done at Screening. Special attention must be paid to liver structure. All abnormalities must be recorded in the eCRF.

6.3.9. Serum Alpha-fetoprotein

Serum alpha-fetoprotein will be measured for all subjects at Screening. The alpha-fetoprotein test is intended to rule out HCC. Samples to be sent to the central laboratory.

6.3.10. Serology, HDV RNA, HCV RNA, and HBeAg Test at Screening

The below listed laboratory tests will be done at central laboratory at Screening:

- HIV antibodies
- HCV antibodies
- HDV antibodies
- HBeAg and HBeAg antibodies
- HBV DNA (for patients not receiving the treatment with nucleoside/nucleotide analogue for chronic HBV infection)

Note: In case of positive HCV antibodies test, HCV RNA (qualitative) test must be done. If the result for HCV RNA test is negative, the patient can be enrolled into the study.

The below listed laboratory test will be done at central virology laboratory at Screening:

HDV RNA

6.4. Efficacy Procedures

If, in the case of external unavoidable circumstances, including COVID-19 pandemic spread in the world, it is not possible for patient to visit the site, upon consent of the patients and by the decision of investigator, the blood sampling may be performed out of the site: at patient's home or laboratory medical office.

6.4.1. Virology Tests

A list of virology tests is given below. These tests will be done by central virology laboratory from frozen samples. Schedule of blood sampling is given in Table 1:

- HDV RNA by quantitative PCR
- HBV DNA by quantitative PCR
- HBsAg levels by quantitative immunoassay
- HBeAg and HBeAg antibodies, only if patient is HBeAg positive at Screening
- HBsAg antibodies

  Note: Blood sampling for HBsAg antibodies should be done as indicated in Table 1. Testing will be done only if HBsAg becomes undetectable.

Instruction for blood sample collection, processing and transport will be given in Laboratory manual.

6.4.2. ALT

The biochemistry sample will be used to obtain ALT results for efficacy assessment as described in Section 6.5.4.

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[redacted]

6.4.4. NTCP Polymorphism and Resistance Tests

Blood samples for determination of NTCP polymorphism are collected at Day 1 for all the patients. NTCP polymorphism will be performed in central laboratory for patient who are either

non-responders or have viral breakthrough defined as below. Details on collection, storage and transportation of samples are provided in laboratory manual.

Sodium-taurocholate cotransporting polypeptide polymorphism will be assessed by partial sequencing of the human genome with the focus on all 5 NTCP exons to determine NTCP polymorphism (SNP Ser267 and others). Single nucleotide polymorphism analysis will be performed to compare patient's NTCP polymorphisms and the respective consensus NTCP sequence.

Blood samples for phenotypic assay are collected at Day 1 for all the patients. Baseline phenotypic assay will be performed in at least 10% of Day 1 samples, in order to determine an half-maximal effective concentration (EC_{50}) threshold at baseline. The five first patients from each treatment arm after randomization will be included into the analysis based on their baseline HDV RNA titer which is supposed to be not less than 1000 IU/mL.

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6.4.5. Serum Alpha-2-Macroglobulin

Test for serum fibrosis marker, alpha-2-macroglobulin, will be done at Randomization/Baseline visit and during the study as indicated in Schedule of Events (Table 1). Enzyme immunoassay analysis will be used.

Samples to be sent to the central laboratory for analysis. Instruction for blood sample collection, processing and transport will be given in Laboratory manual.

6.4.6. Liver Biopsy

It is not necessary to perform liver biopsy at study site for a patient. If agreed with medical monitor and project manager, liver biopsy can be performed at other institution or any other study site.

Liver biopsy samples should be collected if feasible at Screening and Week 48 as indicated in Table 1. If baseline liver biopsy samples are not available (were not provided to central laboratory or were considered as non-evaluable by central laboratory) subsequent liver biopsies should not be performed.

Patients with medical contraindication for liver biopsy are exempt from liver biopsy requirements in this study.

Note: At Screening liver biopsy is performed after confirmation of eligibility. Should the investigator have any doubts regarding patient eligibility, (s)he should contact medical monitor prior to biopsy. If liver biopsy was performed within 1 year prior to Screening, and a patient can provide biopsy records and appropriate biopsy specimens, the available specimens can be used for the baseline evaluation and biopsy at Screening is not required.

Part of the biopsy sample will be used for determination of intrahepatic parameters. Frozen and ambient samples to be sent to the central laboratory for analysis. Instruction for biopsy sample collection, processing, and transport will be given in Laboratory manual.

6.4.7. Transient Elastometry

Transient elastometry (FibroScan) is done at Screening and during the study as indicated in Schedule of Events (Table 1) to assess liver fibrosis staging. The result should be presented in kPa and documented in the eCRF.

It is not necessary to perform the procedure at study site for a patient. If agreed with medical monitor and project manager, FibroScan procedure can be performed at other institution or any other study site.

6.5. Safety Procedures

If, in the case of external unavoidable circumstances, including COVID-19 pandemic spread in the world, it is not possible to collect the blood and urine samples for safety analysis at the site, it can be recommended by the investigator to perform such analysis an any local laboratory for safety control, ie, AEs monitoring.

6.5.1. Physical Examination

A complete physical examination will be performed at Screening, Randomization (V1), Week 24, Week 48, Week 96, and Week 144. A complete physical examination includes evaluation of general appearance, skin, head, eyes, ears, nose and throat, lymph nodes, respiratory, cardiovascular, gastrointestinal including hepatobiliary assessment, musculoskeletal, endocrine system, nervous systems, and urogenital system. At all other visits (Table 1), a symptom directed physical examination is performed.

Any finding present at the screening visit should be reported in the eCRF as medical history and its importance for including the patient into the study must be considered. Any clinically significant worsening of conditions which were present at baseline (last assessment before randomization) or clinically significant worsening as a result of study procedure must be reported as AE in the eCRF.

Assessment of Local Reactions at the Injection Sites.

The investigator will evaluate the injection sites as indicated in Table 1.

In case of any observed clinical abnormalities at the bulevirtide injection sites the investigator should:

- Assess the clinical significance according to the local reaction to injectable product toxicity grading criteria from Table A for “Clinical Abnormalities of the Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials” (Table 3).

- In case of clinical significance (abnormality corresponds to any of the below grade), register it as an AE and record in the source documents and in eCRF the grade according to the local reaction to injectable product toxicity grading criteria from Table A for “Clinical Abnormalities of the Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials” and the grade according to National Cancer Institute (NCI) CTCAE (Version 5.0)

In case of Grade 3 according to the local reaction to injectable product toxicity grading criteria from Table A for “Clinical Abnormalities of the Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials” or above the photo should be taken by the investigator. The photo should be uploaded into eCRF.

Table 3. Tables for Clinical Abnormalities

Reaction to Injectable Product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/ Redness *	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/ Swelling **	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.
** Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

6.5.2. Vital Signs

Blood pressure, heart rate, and body temperature should be measured at Screening and during the study as indicated in Table 1. Vital signs are assessed before study drug administration and at additional times if clinically indicated.

Any finding present at the screening visit should be reported in the eCRF as medical history and its importance for including the patient into the study must be considered. Investigator should assess all results of vital signs assessment that deviate of normal range and investigator should decide whether these deviations qualify as AE or not. See Section 7 for definition and reporting requirements for results of vital signs assessment that qualify as AEs.

Blood pressure and heart rate will be measured after 5 minutes of rest in the supine/sitting position. Systolic and diastolic blood pressure will be measured (mm Hg). All recordings should be made using the same blood pressure recording instrument on the same arm. Heart rate is defined as radial pulse counted for 30 seconds in the supine/sitting position (beats/minute). Respiratory rate is defined as number of breaths counted for 15 seconds in the supine/sitting position (breaths/minute).

Vital signs are entered into eCRF.

6.5.3. Electrocardiogram

A 12-lead ECG will be recorded at Screening and further during the study as indicated in Table 1. Additional assessments could be performed as clinically indicated.

The following parameters will be noted in the eCRF: heart rate, QRS, RR, PQ, QT and QTc intervals. All values should be entered in the eCRF together with a general assessment on whether normal or abnormal and a description of the nature of the abnormality.

Clinically significant deteriorations of ECG parameters compared to Screening should be reported as AEs.

If, in the case of external unavoidable circumstances, including COVID-19 pandemic spread in the world, it is not possible for patient to visit the site, upon consent of the patients and if agreed with medical monitor and project manager, ECG can be performed at other institution or any other study site.

6.5.4. Hematology, Biochemistry, Coagulogram, Vitamin D

Hematology, biochemistry, and coagulogram will be analyzed by central laboratory using standard methods. Schedule of blood sampling is given in Table 1. Additional samples can be taken if samples were considered to be not suitable for analysis at central laboratory or for monitoring of clinically significant abnormalities (eg, Grade 3 or Grade 4 abnormalities according to CTCAE). Additional samples should be also sent to central laboratory.

Instruction for blood sample collection, processing, and transport will be given in Laboratory manual.

Any abnormalities that are discovered at Screening should be further investigated where clinically indicated, in order to ensure that patients are fit to be included in the study and to receive study treatment. Investigator should assess all results of laboratory tests that deviate of normal range and investigator should decide whether these deviations qualify as AE or not. See Section 7 for definition and reporting requirements for results of laboratory tests that qualify as AEs.

Hematology will include:

- Hematocrit
- Hemoglobin
- Platelets
- Reticulocytes
- Red blood cell (RBC) count
- WBC count
- WBC differential (percentage): neutrophils, eosinophils, basophils, monocytes, lymphocytes
- WBC differential (absolute counts): neutrophils, eosinophils, basophils, monocytes, lymphocytes

Coagulogram will include:

- Prothrombin time
- Activated partial thromboplastin time
- International normalized ratio (INR)

Biochemistry (full panel) will include:

- Total protein
- Albumin
- ALT
- AST
- GGT
- P-amylase
- Alkaline phosphatase
- Lipase
- Total bilirubin
- Direct bilirubin
- Total cholesterol
- Creatinine
- Urea
- Glucose
- Potassium
- Sodium
- Chloride
- Phosphorus
- C-reactive protein (CRP)

Biochemistry (abbreviated panel) will include:

- Albumin
- ALT
- AST
- GGT
- Total bilirubin
- Direct bilirubin
- Creatinine
- P-amylase
- Lipase
- CRP

Additionally, level of Vitamin D will be assessed.

6.5.5. Total Blood Bile Salts

Total bile salts will be analyzed by central laboratory. Analysis to be performed at all visits except Screening visit. Instruction for blood sample collection, processing, and transport will be given in Laboratory manual.

6.5.6. Urinalysis

Urinalysis will be performed by central laboratory using standard methods. Schedule of urine sampling is given in Table 1.

The following parameters will be measured:

- pH
- Specific gravity
- Protein
- Glucose
- Bilirubin
- Urobilinogen

- Ketones
- Erythrocytes
- Leukocytes
- Nitrites

Instruction for urine sample collection, processing, and transport will be given in Laboratory manual.

Any abnormalities that are discovered at Screening should be further investigated where clinically indicated, in order to ensure that patients are fit to be included in the study and to receive study treatment. Investigator should assess all results of laboratory tests that deviate of normal range and investigator should decide whether these deviations qualify as AE or not. See Section 7 for definition and reporting requirements for results of laboratory tests that qualify as AEs.

6.5.7. Adverse Events

See Section 7.

6.6. Other Procedures

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6.6.2. Pharmacokinetics

Bulevirtide concentration will be measured throughout the study to investigate the possible bulevirtide accumulation. Analysis will be done by central laboratory.

Blood samples will be collected at Randomization/Baseline visit and all Treatment visits after the start of bulevirtide therapy as indicated in Table 1. Sampling should be done 1 hour ± 15 min after bulevirtide injection. During first 48 weeks pharmacokinetics samples will be collected only for Arms B and C.

Frozen samples to be sent to the central laboratory for analysis. Instruction for blood sample collection, processing and transport will be given in Laboratory manual.

6.7. Patient Diary

All patients will be given a Patient Diary to register the following information over the course of the treatment:

- Date and time of each bulevirtide dosing
- AEs experienced by a patient

Paper Patient Diary includes detachable sections for each visit. At each visit to the study site as indicated in Table 1, completed Patient Diary parts will be teared of and collected.

Patients randomized to Arm A will be given a Patient Diary at Week 48.

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6.9. Liver Related Clinical Events

Investigators should closely monitor the following liver-related clinical events starting from the randomization, including, but not limited to: cirrhosis development; development or worsening jaundice, coagulopathy, ascites, hepatic encephalopathy; bleeding from esophageal varices; HCC development; liver transplantation; liver related hospitalization: number of hospitalizations and duration of each hospitalization; liver related death. In case of such event onset it will be recorded in eCRF and registered as AE/SAE. See Section 7.1.3.

7. ADVERSE EVENTS

7.1. Definitions

7.1.1. Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH E2A).

NOTE: Conditions that existed before randomization (eg, ALT elevation before randomization) should not be reported as AE unless a notable deterioration has occurred or SAE has occurred after signature of informed consent.

7.1.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,

NOTE:

The term “life-threatening” refers to an event in which the subject is at immediate risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization,

NOTE:

An event that leads to hospitalization under the following circumstances should not be reported as an AE or an SAE:

- Hospitalization for respite care,
- Planned hospitalization required by the protocol (eg, planned hospitalization for conducting liver biopsy),
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
  - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease,

— The patient has not experienced an AE,

An event that leads to hospitalization under the following circumstances is not considered to be an SAE, but should be reported as an AE instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours.
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

When an SAE occurs, the investigator is required to follow the procedures described in Section 7.3.3.

7.1.3. Adverse Event of Special Interest (AESI)

An AESI is a noteworthy event for the study drug that should be monitored closely. It could be either serious or non-serious.

7.1.3.1. Local Reactions at the Bulevirtide Injection Site

Local reactions at the bulevirtide injection site belong to AESI that will be actively monitored during the study.

Refer to the Section 6.5.1 for requirements on assessment and registration of local reactions at the injections site.

7.1.3.2. Liver Related Adverse Events

Investigators should closely monitor the following liver-related clinical events starting from the randomization, including, but not limited to: cirrhosis development; development or worsening jaundice, coagulopathy, ascites, hepatic encephalopathy; bleeding from esophageal varices; HCC development; liver transplantation; liver related hospitalization: number of hospitalizations and duration of each hospitalization; liver related death. In case of such event onset it will be recorded in eCRF and registered as AE/ SAE. Ascertaining whether an AE is considered liver related should be as per the investigator opinion.

7.1.4. Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an AE. A laboratory test result must be reported as an AE if it meets any of the following criteria:

- Is accompanied by clinical symptoms,
- Results in a change in study treatment (eg, treatment interruption, or treatment discontinuation),
- Results in a medical intervention (eg, potassium supplementation for hypokalemia), a change in concomitant therapy or close medical monitoring,
- Is clinically significant in the investigator's judgment.

NOTE: Bulevirtide increases total bile salts level and this effect is related to the primary mechanism of action of bulevirtide. If isolated increase of total bile salts level above the upper limit of normal is both asymptomatic and judged by investigator to be clinically insignificant it should not be reported as AE.

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (eg, alkaline phosphatase and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (ie, cholestasis) should be recorded on the AE form in the eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the AE eCRF. If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the AE.

7.1.5. Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an AE. A vital sign result must be reported as an AE if it meets any of the following criteria:

- Is accompanied by clinical symptoms,
- Results in a change in study treatment (eg, treatment interruption, or treatment discontinuation),
- Results in a medical intervention, change in concomitant therapy or close medical monitoring,
- Is clinically significant in the investigator's judgment.

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an AE.

7.1.6. Adverse Drug Reaction (ADR)

In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, ie, the relationship cannot be ruled out.

7.1.7. Unexpected Adverse Drug Reaction

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, investigator's brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product) (ICH E6).

7.1.8. Suspected Unexpected Serious Adverse Reaction (SUSAR):

Serious ADR that is classified as unexpected, ie, a serious adverse reaction, the nature and severity of which is not consistent with the applicable product information (investigator's brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

7.2. Classification of an Adverse Event

7.2.1. Severity of Event

The severity of the AE should follow the NCI CTCAE (Version 5.0), and the highest level of severity that the AE reached should be entered in the eCRF.

A copy of the CTCAE Version 5.0 can be downloaded from the following web site

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

If a CTCAE term cannot be found, grade must be assigned as follows:

Grade	Severity	Definition
Grade 1	Mild	Discomfort noticed but no disruption of normal daily activity.
Grade 2	Moderate	Discomfort sufficient to reduce or affect daily activity; no treatment or medical intervention is indicated although this could improve the overall well-being or symptoms of the patient.
Grade 3	Severe	Inability to work or perform normal daily activity; treatment or medical intervention is indicated in order to improve the overall well-being or symptoms; delaying the onset of treatment is not putting the survival of the patient at direct risk.
Grade 4	Life-threatening/ disabling	An immediate threat to life or leading to a permanent mental or physical conditions that prevents work or performing normal daily activities; treatment or medical intervention is required in order to maintain survival.
Grade 5	Death	AE resulting in death.

If severity of AE changed during the course of development of the event, the maximum severity is reported.
Refer to the Section 6.5.1 for requirements on severity assessment of local reactions at the bulevirtide injections site.

7.2.2. Relationship to Study Medication

For all collected AEs, the investigator who examines and evaluates the patient will evaluate whether there is a reasonable causal relationship between the occurrence of the AE and the exposure to the study drug(s) and/or clinical trial protocol procedure(s). Medical judgment should be used to determine the relationship, considering all relevant factors including the pattern of reaction, temporal relationships, positive dechallenge or rechallenge, relevant medical history, and confounding factors such as co-medication or concurrent diseases.

The expression "reasonable causal relationship" is meant to convey in general that there are factor arguments to suggest a causal relationship (ICH E2A, Section IIIA 1).

The relationship assessment for an AE is to be completed using the following definitions as a guideline for all AEs occurring during this clinical trial.

Reasonable Possibility:

According to the reporting investigator, there is a reasonable possibility (ie, suggestive evidence or arguments) that there is a causal relationship irrespective of the dose administered

- Between the study drug and the AE, and/or
- Between the clinical trial protocol procedure and the AE

No Reasonable Possibility:

No suggestive evidence or arguments can be identified regarding a causal relationship between the study drug or the clinical trial protocol procedure and the AE.

7.2.3. Adverse Event Outcome

The outcome is the information on recovery and any sequelae.

Outcome	Definition
Not recovered/not resolved:	The AE still persists.
Recovered/resolved:	The AE is resolved.
Recovered/ resolved with sequelae:	The patient is stabilized, but with sequelae from this AE
Recovering/resolving:	The patient is recovering from this AE/this AE is resolving.
Fatal:	The patient died as a result of this AE
Unknown:	The outcome of this AE is not known.

7.2.4. Adverse Event Assessment and Follow-up

Information to be collected includes event description, date and time of onset, clinician's assessment of severity, seriousness, relationship to study product, study procedures, other therapy and underlying disease, action taken and date of resolution/stabilization of the event with

AE outcome. Adverse Events assessed as related to the study drug and/or procedure will be monitored until they have resolved or reached a stable condition, with or without sequelae. Other AEs will be monitored until the last visit if they have not resolved or reached a stable condition. AEs will be characterized as intermittent if interval between the events with the same term does not exceed two days. For such AEs documentation of first episode onset and the last episode end date is required.

7.3. Reporting Procedure

7.3.1. Adverse Event Reporting Period

Investigators will seek information on AEs at each patient contact. All AEs, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the AE eCRF.

Reporting period for SAEs starts after informed consent has been obtained and ends at the End of Study visit. These SAEs include events caused by a protocol-mandated intervention (eg, invasive procedures such as biopsies, discontinuation of medications). If SAE is considered to be related to the study drug or study procedures it must be reported to the sponsor regardless of the reporting period. For information on reporting of SAEs to sponsor see Section 7.3.3.

Reporting period for non-serious AEs starts with the randomization and ends at the End of Study visit. Non-serious AEs at Screening period which are in the investigator's opinion related to study procedures (eg, biopsy) also should be reported.

7.3.2. Adverse Event Reporting

A consistent methodology of non-directive questioning should be adopted for eliciting AE information. Example of non-directive question:

> "How have you felt since your last clinic visit?"

Any AE occurring during the AE reporting period, whether or not related to the study drug and/or study procedure, will be recorded immediately in the source document, and described on the AE form of the eCRF along with the date and time of onset, seriousness, severity, relationship to the study drugs and/or study procedure and/or other therapy and/or underlying disease, action taken, and outcome with the date of resolution/stabilization of the event, if applicable, without omitting any requested and known information.

AEs assessed as related to the study drug and/or procedure will be monitored until they have resolved or reached a stable condition, with or without sequalae. Other AEs will be monitored until the last visit if they have not resolved or reached a stable condition.

Reporting procedures for SAEs (see Section 7.3.3), AESIs (see Section 7.4), and pregnancies (see Section 7.5) must be followed.

7.3.3. Serious Adverse Event Reporting

For any SAE occurring during the clinical trial, regardless of whether or not related to the study drug and/or procedure, the investigator must:

1) Take prompt and appropriate medical action, if necessary.

2) Ensure that the event is evaluated as an SAE.

3) **Immediately** complete the paper SAE form, compile any relevant information or anonymized medical records (eg, laboratory test results) and send it via email or by fax within 24 hours of receipt of this relevant information to:

Contact information for Investigator's notification in case of SAEs

Gilead Global Patient Safety

Email: PPD

or

Fax: PPD

NOTE: Before sending the SAE report, please inform CRA by telephone.

4) Complete the AE form in the eCRF. As soon as the event is saved as serious, an email alert will be sent to predefined recipients to highlight that an SAE has occurred.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or reached a stable condition. For all additional follow-up evaluations, the paper SAE form must be completed and sent via email or by fax to Gilead Global Patient Safety within 24 hours of receipt of the updated information. Other supporting documentation of the event may be requested by the study sponsor and should be provided as soon as possible, within 24 hours of receipt of the updated information. As soon as it is possible to do so, any SAE reported via paper must be transcribed onto the AE eCRF. Whenever an SAE is updated in eCRF, a new email alert will be sent.

When the outcome of the event is known, an updated SAE form must be completed and sent via email or fax to Gilead Global Patient Safety.

The study sponsor will be responsible for reporting to the competent authorities in all the Member States concerned of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible (without delay) but in no case later than 7 calendar days after the sponsor's initial receipt of the information, and no later than 15 days for other suspected unexpected serious adverse reaction. The sponsor will inform all the investigators of the occurrence of any SUSAR during the clinical conduct of the study.

7.4. Events of Special Interest

See Section 7.1.3.

7.5. Hepatic Safety Adjudication Committee

A Hepatic Safety Adjudication Committee (HSAC) will be implemented to assess all severe and SAEs related to Hepatobiliary system and other significant safety issues as considered necessary by sponsor.

7.6. Reporting of Pregnancy

Any pregnancy occurring during clinical trials, must be monitored until its outcome in order to ensure the complete collection of safety data.

If a subject becomes pregnant, the investigator must:

- Withdraw the subject from the clinical trial.
- Complete as fully as possible Paper Pregnancy Report form and/or Pregnancy Outcome Report form (as applicable).
- Send the paper form via email or by fax within 24 hours of receipt of the information to:

Gilead Global Patient Safety

Email: PPD

or

Fax: PPD

- Complete the Pregnancy Report form in eCRF. Email alert will be sent to predefined recipients to highlight that a pregnancy has occurred.

If the pregnancy leads to an abortion (spontaneous abortion or therapeutic abortion), in utero death or congenital anomaly, follow the procedure for declaration of an SAE (see Section 7.3.3). Other cases, such as reports of induced termination of pregnancy without information on congenital malformation, reports of pregnancy exposure without outcome data, or reports which have a normal outcome should not be submitted as SAE.

If a female partner of a male subject receiving/received bulevirtide becomes pregnant, the investigator should propose signing of the Information Sheet for pregnant partner and ICF to the provision of information about pregnancy and its outcome.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Populations

Enrolled Set: All patients screened and enrolled into this study.

Randomized Set: All enrolled and randomized patients.

Full Analysis Set (FAS): All patients randomized to delayed treatment arm or randomized to bulevirtide and received bulevirtide at least once after randomization.

Per-protocol (PP) Set: All patients of the FAS whom no protocol deviations are judged to have an impact on the analysis of the primary efficacy endpoint of combined response (or on secondary efficacy endpoint of SVR24 at follow-up Week 24 [FU-24], ie study Week 168). Details will be specified in the statistical analysis plan (SAP) and final decision on exclusion from PP set will be made in a data review meeting before database lock.

Safety population: All patients randomized to delayed treatment arm or randomized to bulevirtide and received bulevirtide at least once after randomization.

8.2. Description of Statistical Methods

8.2.1. Demographic and Baseline Measurements

All demographic and background characteristic variables will be summarized by treatment group and overall to describe the study population.

The data will be presented for all patients in the FAS.

8.2.2. Analysis of Efficacy

Continuous variables will be summarized in terms of descriptive statistics including number of observations, mean, standard deviation, minimum, maximum and quartiles. Categorical variables will be summarized in terms of frequencies and percentages. Where data are collected over time, both the observed data and the change from baseline will be summarized by treatment group at each time point.

Primary Analysis:

The primary endpoint of this study is the response rates at Week 48 where response is defined as undetectable HDV RNA or decrease by ≥ 2 $\log_{10}$ IU/mL from baseline combined with ALT level within reference range. Two two-sided Fisher tests at an overall significance level of 0.05 will be performed to sequentially test the hypotheses

H_{01}: $p_O = p_{M10mg}$ vs H_{11}: $p_O \neq p_{M10mg}$

H_{02}: $p_O = p_{M2mg}$ vs H_{12}: $p_O \neq p_{M2mg}$

where p_O, p_{M2mg} and p_{M10mg} are the expected response rate for delayed treatment arm, bulevirtide 2 mg and bulevirtide 10 mg, respectively. Patients with missing assessment at 48 weeks in the primary endpoint will be handled as non-responders unless it is related to COVID-19 in which case missing values will be imputed using the last observation carried forward (LOCF) approach. In terms of a hierarchical testing procedure, the second null hypothesis will not be rejected if the first null hypothesis could not be rejected. Confidence intervals (CIs) with confidence probability adjusted to the respective significance levels using exact unconditional confidence limits based on the score statistic will be presented for the rate differences. Clopper-Pearson 95%-CIs will be calculated for the single rates.

An interim analysis will be performed on the response rates at Week 24. To account for the repeated analysis of response the nominal two-sided significance level will be split among the time points with 0.01 for 24 weeks and 0.04 for 48 weeks.

The primary analysis will be based on the FAS. The analysis will be repeated for the PP set and in case of differences between the FAS and the randomized set also for the randomized set to assess consistency and robustness of results.

Due to the expected low number of responders under delayed treatment the analysis will not be stratified by covariables. The effect of region and the presence of liver cirrhosis will be analyzed descriptively.

Key Secondary Analysis

The proportion of patients with undetectable HDV RNA at Week 48 is the key secondary endpoint and will be used to test differences between the bulevirtide doses and hence evaluate the dose response relationship. Patients with missing assessment at 48 weeks in undetectable HDV RNA will be handled in the same way as the primary endpoint described above.

A two-sided Fisher tests will be performed to test the hypotheses

$$H_{03}: r_{M2mg} = r_{M10mg} \text{ vs } H_{13}: r_{M2mg} \neq r_{M10mg}$$

where r_{M2mg}, r_{M10mg} are the expected rates of patients with undetectable HDV RNA for bulevirtide 2 mg and bulevirtide 10 mg, respectively.

Continuing the hierarchical testing procedure used for the primary endpoint this test will only be performed if both primary null hypotheses have been rejected. Otherwise null hypothesis H_{03} will not be rejected. To maintain control of the family-wise error rate the same nominal levels of significance will be employed that was used for the primary analyses.

CIs with confidence probability adjusted to the respective significance levels using exact unconditional confidence limits based on the score statistic will be presented for the rate differences. Clopper-Pearson 95%-CIs will be calculated for the single rates.

The same methods will be applied at the interim analysis on response at Week 24.

Other Secondary Analyses

All other efficacy data will be analyzed descriptively.

Rates of patients with ALT normalization at Week 48, undetectable HDV RNA 24 and 48 weeks after scheduled end of treatment (sustained virological response) will be analyzed analogously to the primary endpoint in the framework of explorative analysis without adjusting for multiple testing. Patients with missing assessment at 48 weeks in the other secondary endpoints CCI [redacted] will be handled as non-responder, regardless the reason for the absence.

Change from baseline in liver stiffness as measured by elastography will be analyzed in a mixed effect repeated measurement model (MMRM) with fixed-effect factors treatment, region, presence of cirrhosis, visit and treatment-by-visit interaction and the baseline values as covariable. CIs will be based on estimated means (least square means) and corresponding t-statistics. Restricted maximum likelihood (REML) will be employed to fit the model for primary analysis. Within-patient variation will be modeled as random effect with unstructured covariance structure. The Kenward-Roger (35) approximation will be used to estimate the denominator degrees of freedom. If the model still fails to converge, the model will be fit using covariance matrices of the following order specified by a decreasing number of covariance parameters until convergence is met: heterogeneous Toeplitz, heterogeneous autoregressive, Toeplitz, and autoregressive.

Patients receiving nucleoside/nucleotide analogues will be subject to an additional descriptive subgroup analysis.

CCI [redacted]

[redacted]

8.2.3. Analysis of Safety

Adverse Events

Adverse events will be coded using MedDRA and will be presented by primary SOC and PT. The analysis will focus on the treatment-emergent AEs (TEAE), ie, AEs which started or worsened after randomization (delayed treatment group) or after start of treatment (bulevirtide groups) and no later than 30 days after permanent discontinuation of treatment. The frequency of TEAEs will be summarized by incidences. In these summaries, each patient will be counted only once within each PT and SOC.

Frequencies of TEAEs will also be presented by relationship to study treatment and by maximum severity. Additional analyses will be performed for SAE, TESAE and AEs leading to discontinuation.

Vital Signs

Vital signs will be described by summary statistics for measured values and changes from baseline by visit.

Laboratory Parameters

Laboratory parameters will be described by summary statistics for measured values and changes from baseline by visit.

The clinical assessment of laboratory variables (abnormal high/clinically relevant, abnormal high/not clinically relevant, within normal limits, abnormal low/not clinically relevant, abnormal low/clinically relevant) will be tabulated by visit for each clinical laboratory analyte in frequency tables. Additionally, for each laboratory parameter shifts in assessments from baseline to Week 48 and Week 96 visit will be presented (shift tables).

Electrocardiogram

The ECG assessment summary categories will be tabulated by visit. Additionally, shifts in assessments from baseline to visits will be presented (shift tables).

Descriptive summaries of actual values and changes from baseline will be presented for ECG measures of PR interval, QRS interval, QT interval, QT-interval corrected for heart rate (QTc, Bazett), and heart rate by visit.

Also, the number and percent of patients in each treatment group with QTc values 451 – 480 ms, 481 - 500 ms or > 500 ms and the number and percent of patients in each treatment group who experienced a change versus baseline > 30 ms or a change > 60 ms will be presented by visit.

Other Safety Assessments

The number and percentages of patients with normal/abnormal findings in physical examinations as well as with production of bulevirtide antibodies will be presented by visit.

8.2.4. Determination of Sample Size

The primary analysis of the study will be the separate comparisons of bulevirtide 2 mg and bulevirtide 10 mg with delayed treatment after a period of 48 weeks, respectively. The primary endpoint is defined as the response rate at Week 48 measured by undetectable HDV RNA or a decrease by ≥ 2 $\log_{10}$ IU/mL from baseline combined with normal ALT values within the reference range. The overall significance level will be 0.05. An interim analysis will be performed on the response rates at Week 24. To account for the repeated analysis of response the nominal two-sided significance level will be split among the time points with 0.01 for 24 weeks leaving 0.04 for 48 weeks. At each time point the bulevirtide doses will be compared to delayed treatment in terms of a hierarchical testing procedure starting with the higher dose at the respective adjusted two-sided significance levels.

The expected response rates at 48 weeks for the bulevirtide 2-mg and 10-mg doses are 45% or greater. The conservative expectation for the delayed treatment response rates are 8% or less. These assumptions are based on results from preceding Phase 2 study (MYR202).

With a sample size of 47 patients per treatment group a Fisher's exact test with a 0.04 two-sided significance level will have 97.8% power to detect this difference between the bulevirtide 10 mg and the delayed treatment proportions and between the bulevirtide 2 mg and the delayed treatment proportions. The power to reject both null hypotheses simultaneously will be 95.6%.

This sample size will be slightly increased to 50 patients per treatment group to account for a few potential early withdrawals before exposure.

Hence 150 patients will be randomized.

8.2.5. Interim and Final Analyses

Analyses of data are planned to be performed at following times:

1) When all patients complete visit at Week 24 or discontinue the study (interim analysis).

2) When all patients complete visit at Week 48 or discontinue the study (primary endpoint analysis).

CCI [redacted]

6) When all patients complete visit at Week 240 or discontinue the study (final analysis: CCI [redacted] of all collected data of the study).

Procedures for maintaining the overall significance level of 0.05 during first and second data analyses are described above (see Section 8.2.2).

CCI [redacted]

Any deviation(s) from the original statistical plan will be described and justified in protocol and/or in the final report, as appropriate.

9. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Source data are all information, original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, participant evaluation checklists, recorded data from automated instruments, participant files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical study.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available. The eCRF is essentially considered a data entry form and should not constitute the original (or source) medical records unless otherwise specified.

The investigator is responsible for maintaining source documents.

Direct access to source data and documents must be provided to the study medical monitor, sponsor's CRA and authorized representatives (contract research organization [CRO]), sponsor's/CRO's auditor, regulatory inspectors, members of ethics committees and representatives of insurance companies.

10. QUALITY ASSURANCE AND QUALITY CONTROL

10.1. Periodic Monitoring

Monitoring will be done by the CRAs according to standard operation procedures and Monitoring Plan. At the beginning of the trial the responsible CRA will perform an Initiation visit at the investigational site (prior to the inclusion of the first study participant). During regular on-site visits the CRA will review the entries into the eCRFs on the basis of applicable source documents. The investigators must allow the CRA to verify all essential documents and must provide support to the CRA at any time. Frequency of monitoring will be defined in the Monitoring Plan. By frequent communications (letters, telephone, fax), the CRA will ensure that the study is conducted according to the protocol and regulatory requirements.

In the case of external unavoidable circumstances, including COVID-19 pandemic spread in the world, on-site visit is not possible, remote monitoring will be performed, given that all regulatory and essential data protection requirements are met and appropriate arrangements to ensure patients' personal data protection and confidentiality are taken. Such remote monitoring can be performed, for example, using telephone contacts or video conferences, provided that source documents or records with personal data of the study participants may not leave the study site, not even as a copy, and therefore no permanent storage outside the study site may take place.

10.2. Audit and Inspection

Competent and local authorities and an auditor authorized by the sponsor may request access to all source documents, eCRF, and other trial documentation. Direct access to these documents must be guaranteed by the investigators who must provide support at all times for these activities. In case inspections will be announced to the principal investigator, the sponsor and the CRA should be informed in time.

11. ETHICS/PROTECTION OF HUMAN SUBJECTS

11.1. Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Declaration of Helsinki and the ICH E6 (GCP).

11.2. Independent Ethics Committee and/or Institutional Review Board

The protocol, ICF(s), recruitment materials, and all participant materials will be submitted to the IEC/IRB for review and approval. Approval of both the protocol and the ICF must be obtained before any participant is enrolled. Any substantial amendment to the protocol will require review and approval by the IEC/IRB before the changes are implemented to the study. Any amendment to the protocol deemed by the sponsor as "substantial" will be submitted to the regulatory authority for notification and approval. All changes to the ICF will be IEC/IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

11.3. Informed Consent Process

Consent forms describing in detail the study medications, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting any study procedures.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants. Consent forms will be IEC/IRB approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

In the case of external unavoidable circumstances, including COVID-19 pandemic spread in the world, it is not possible for patient to visit the site, however, any urgent measures need to be implemented in the interest of patient's safety, informed consent can be received in form of the participant's oral consent by phone supplemented with an email confirmation (if it is possible) before the respective action. Updated patient information sheet and ICF should be signed at the subsequent visit, where applicable. Any consent obtained this way should be documented clearly.

11.4. Participant and Data Confidentiality

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor and their agents. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The CRA, other authorized representatives of the sponsor, representatives of the IEC/IRB or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the authorized CRO/Data Management company. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by authorized CRO/Data Management company will be secured and password protected.

12. DATA HANDLING AND RECORD KEEPING

12.1. The Entering of Data into the eCRF

All data must be entered in English. The eCRFs should always reflect the latest observations on the patients participating in the study. Therefore, the eCRFs should be completed as soon as possible during or after the patient's visit. To avoid inter-observer variability, every effort should be made to ensure that the same individual who made the initial baseline determinations completes all corresponding follow-up evaluations. The investigator must verify that all data entries in the eCRFs are accurate and correct. If some assessments are not done, or if certain information is not available, not applicable or unknown, this should be indicated in the eCRF. The investigator will be required to electronically sign off the clinical data.

12.2. The Query Process

The monitor will review the eCRFs and evaluate them for completeness and consistency. Each eCRF will be compared with the respective source documents to ensure that there are no discrepancies between critical data. All entries, corrections, and alterations are to be made by the investigator or designee. The monitor cannot enter data in the eCRFs. Once clinical data have been submitted to the central server via the eCRF, corrections to the data fields will be audit trailed, meaning that the reason for change, the name of the person who made the change, together with time and date will be logged. Roles and rights of the site personnel responsible for entering clinical data into the eCRF will be determined in advance. If additional corrections are needed, the responsible monitor or Data Manager will raise a query in the electronic data capture application. The appropriate study personnel will answer the queries in the eCRF. This will be audit trailed by the electronic data capture application meaning that the name of study personnel, time, and date are logged.

12.3. Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical study staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. Do not erase, overwrite, or use correction fluid or tape on the original.

Data reported in the eCRF derived from source documents should be consistent with the source documents.

The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

12.3.1. User ID

eCRF records will be automatically appended with the identification of the creator, by means of their unique User ID. Specified records will be electronically signed by the investigator to document his/her review of the data and acknowledgement that the data are accurate. This will be facilitated by means of the investigator's unique User ID and password; date and time stamps will be added automatically at time of electronic signature. If an entry in an eCRF requires change, the correction should be made in accordance with the relevant software procedures.

12.3.2. Audit Trail

All changes in the eCRF will be fully recorded in a protected audit trail, and a reason for the change will be required.

12.4. Study Records Retention

Study documents should be retained until at least 15 years have elapsed since the study completion. These documents should be retained for a shorter or longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable.

12.5. Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or manual of procedures requirements (if applicable). The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, Sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, Section 5.1.1
- 5.20 Noncompliance, Sections 5.20.1, and 5.20.2.

It is the responsibility of the site to use continuous vigilance to identify and report deviations. Protocol deviations must be sent to the local IEC/IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IEC/IRB requirements.

All protocol deviations related to COVID-19 should be classified as "COVID-19 related" and described in the clinical study report.

12.6. Publication and Data Sharing Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

13. FINANCING AND INSURANCE

13.1. Financing

The sponsor financially supports the study. The company will deliver the study drugs free of charge as well as paying the investigator/ investigational sites a fee for the patients enrolled to cover trial costs.

13.2. Insurance

According to applicable national laws and EU regulations, an insurance policy has to be subscribed covering in its terms and provisions the legal liability for injuries caused to participating persons and arising out of this research performed strictly in accordance with the scientific protocol as well as with applicable law and professional standards.

14. LITERATURE REFERENCES

1. Radjef, N., Gordien, E., Ivaniushina, V. et al. Molecular phylogenetic analyses indicate a wide and ancient radiation of African hepatitis delta virus, suggesting a *Deltavirus* genus of at least seven major clades. J Virol. 2004; 78(5):2537-44.
2. Taylor, J. Hepatitis delta virus. Virology. 2006; 344(1):71-6.
3. Niro, G., Smedile, A. Current concept in the pathophysiology of hepatitis delta infection. Curr Infect Dis Rep. 2012; 14(1):9-14.
4. Niro, G., Gravinese, E., Martini, E. et al. Clearance of hepatitis B surface antigen in chronic carriers of hepatitis delta antibodies. Liver. 2001; 21(4):254-9.
5. Cole, S., Gowans, E., Macnaughton, T. et al. Direct evidence foe cytotoxicity associated with expression of hepatitis delta virus antigen. Hepatology. 1991; 13(5):845-51.
6. Lacombe, K., Boyd, A., Desvarieux, M. et al. Impact of chronic hepatitis C and/or D on liver fibrosis severity in patients co-infected with HIV and hepatitis B virus. AIDS. 2007; 21(18):2546-9.
7. Zachou, K., Yurdaydin, C., Drebber, U. et al. Quantitative HBsAg and HDV-RNA levels in chronic delta hepatitis. Liver Int. 2010; 30(3):430-7.
8. Verme, G., Amoroso, P., Lettieri, G. et al. A histological study of hepatitis delta virus liver disease. Hepatology. 1986; 6(6):1303-7.
9. Yurdaydın, C., Idilman, R., Bozkaya, H., Bozdayi, A. Natural history and treatment of chronic delta hepatitis. J Viral Hepat. 2010; 17(11):749-56.
10. Wedemeyer, H. Re-emerging interest in hepatitis delta: new insights into the dynamic interplay between HBV and HDV. J Hepatol. 2010; 52(5):627-9.
11. Rizzetto, M. Hepatitis D: thirty years after. J Hepatol. 2009; 50(5):1043-50.
12. Wedemeyer, H., Manns, M. Epidemiology, pathogenesis and management of hepatitis D: update and challenges ahead. Nat Rev Gastroenterol Hepatol. 2010; 7(1):31-40.
13. de Man, R., Sprey, R., Niesters, H. et al. Survival and complications of a cohort of patients with anti-Delta positive liver disese presenting in a tertiary referral clinic. J Hepatol. 1995; 23(6):662-7.
14. Gaeta, G., Stroffolini, T., Chiaramonte, M., et al. Chronic hepatitis D: a vanishing Disease? An Italian multicenter study. Hepatology. 2000; 32(4 Pt 1):824-7.
15. Manesis, E., Vourli, G., Dalekos, G. et al. Prevalence and clinical course of hepatitis delta infection in Greece: a 13-year prospective study. J Hepatol. 2013; 59(5): 949-56.
16. Romeo, R., Del Ninno, E., Rumi, M.et al. A 28-year study of the course of hepatitis Delta

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

17. Buti, M., Homs, M., Rodriguez-Frias, F. Clinical outcome of acute and chronic hepatitis delta over time: a long-term follow-up study. J Viral Hepat. 2011; 18(6):432-42.
18. Heidrich, B., Manns, M., Wedemeyer, H. Treatment options for hepatitis delta virus infection. Curr Infect Dis Rep. 2013; 15(1):31-8.
19. Niro, G., Smedile, A., Ippolito, A. et al. Outcome of chronic delta hepatitis in Italy: a long-term cohort study. J Hepatol. 2010; 53(5):834-40.
20. Cornberg, M., Protzer, U., Dollinger, M. et al. Prophylaxis, Diagnosis and Therapy of Hepatitis-B-Virus-(HBV-) Infection: upgrade of the guideline, AWMF-Register 021/011. Z Gastroenterol. 2007; 45(6):525-74.
21. Gish, R., Yi, D., Kane, S. et al. Coinfection with hepatitis B and D: epidemiology, prevalence and disease in patients in Northern California. J Gastroenterol Hepatol. 2013; 28(9):1521-5.
22. Kucirka, L., Farzadegan, H., Feld, J. et al. Prevalence, correlates and viral dynamics of hepatitis delta among injection drug users. J Infect Disease. 2010; 202(6):845-52.
23. European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2017; 67(2):370-98.
24. European Association for the Study of the Liver. EASL clinical practice guidelines: Management of chronic hepatitis B virus infection. J Hepatol. 2012; 57:167-85.
25. Triantos C., Kalafateli M., Nikolopoulou V., Burroughs A. Meta-analysis: antiviral treatment for hepatitis D. Aliment Pharmacol Ther. 2012; 35:663-73.
26. Heidrich, B., Yurdaydın, C., Kabaçam, G. et al. Late RNA HDV relapse after peginterferon alfa-based therapy of chronic hepatitis delta. Hepatology. 2014; 60(1):87-97.
27. Wranke A., Serrano B.C., Heidrich B. et al. Antiviral treatment and liver-related complications in hepatitis delta. Hepatology. 2017; 65:414-25.
28. Karaca C., Soyer O.M., Baran B. et al. Efficacy of pegylated interferon-α treatment for 24 months in chronic delta hepatitis and predictors of response. Antivir Ther. 2013; 18:561-66.
29. Heller T., Rotman Y., Koh C. et al. Long-term therapy of chronic delta hepatitis with peginterferon alfa. Aliment Pharmacol Ther. 2014; 40:93-104.
30. Wedemeyer, H., Yurdaydin, C., Ernst, S., et al. HIDIT-2 Study Group. Prolonged therapy of hepatitis delta for 96 weeks with pegylated-interferon-α-2a plus tenofovir or placebo does not prevent HDV RNA relapse after treatment: the HIDIT-2 study. J Hepatol. 2014; 60(1):S2–S3.
31. Guideline on the clinical evaluation of medicinal products intended for treatment of hepatitis B. CHMP/EWP/6172/03, 23 February 2006.

32. MYR202, Interim Clinical Study Report, Version 1.0 dated 10 May 2018.

33. Terrault N, Lok A, McMahon B, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018 Apr;67(4):1560-1599.

34. European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2017 Aug;67(2):370-398.

35. Kenward, M. and Roger, J. (1997). Small Sample Inference for Fixed Effects from Restricted Maximum Likelihood. Biometrics 53, 983-997.

36. http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm#classInhibit (Table 5.1).

37. Nakanishi T, Tamai I. Genetic polymorphisms of OATP transporters and their impact on intestinal absorption and hepatic disposition of drugs. Drug Metab Pharmacokinet 2012;27:106-21.

38. Smith NF, Figg WD, Sparreboom A. Role of the liver-specific transporters OATP1B1 and OATP1B3 in governing drug elimination. Expert Opin Drug Metab Toxicol 2005;1:429-45.

39. Talavera Pons S, Boyer A, Lamblin G, Chennell P, Châtenet FT, Nicolas C, Sautou V, Abergel A. Managing drug-drug interactions with new direct-acting antiviral agents in chronic hepatitis C. Br J Clin Pharmacol 2017;83:269-293.

APPENDIX 1. CONFIRMATION OF PATIENTS' ELIGIBILITY

Inclusion Criteria		Confirmation
1	Provision of signed and dated informed consent form	Signed and dated informed consent form and documented medical record
2	Male or female, aged 18-65 years (inclusive)	Documented by investigator in medical record
3	Positive serum anti-HDV antibody results or PCR results for serum/ plasma HDV RNA for at least 6 months before Screening	Copy of lab test report or copy of discharge
4	Positive PCR results for serum/ plasma HDV RNA at Screening	Central Lab test report
5	Alanine aminotransferase level >1×ULN, but less than 10 × ULN	Central Lab test report
6	Serum albumin >28 g/L	Central Lab test report
7	Negative urine pregnancy test for females of childbearing potential	Urine pregnancy test result at site documented in medical records
8	Female subject: Postmenopausal for at least 2 years	Assessed and documented by investigator in medical record
	Female subject: Surgically sterile (total hysterectomy or bilateral oophorectomy, bilateral tubal ligation, staples, or another type of sterilization)	
	Female subject: Abstinence from heterosexual intercourse throughout the study	
	Female subject: Willingness to use highly effective contraception (double barrier method or barrier contraception in combination with hormonal or intrauterine contraceptive) throughout the study and for 3 months after the last dose of the study medication for patients discontinued during the treatment period	
9	Male subjects must agree to use a highly effective contraception (double barrier method or barrier contraception in combination with hormonal or intrauterine contraceptive used by female partners) and not to donate sperm throughout the study and for 3 months after the last dose of the study medication for patients discontinued during the treatment period	Assessed and documented by investigator in medical record

Exclusion Criteria		Confirmation
1	Child-Pugh hepatic insufficiency score over 7 points. Uncomplicated oesophageal varices allowed; Subjects with current bleeding or ligation, or history of bleeding or ligation within the last 2 years are excluded.	Assessed and documented by investigator in medical record
2	HCV or uncontrolled HIV coinfection. Subjects with HCV antibodies can be enrolled, if screening HCV RNA test is negative. Subjects with HIV infection can be enrolled if CD4+ cell counts are >500/mL and HIV RNA is below limit of detection for at least 12 months.	HCV: Central Lab test report HIV: Copy of lab test report or copy of discharge with the results for HIV RNA (quantitative) and CD4+ count at least 12 months before Screening and at least 1 month before Screening
3	Creatinine clearance < 60 mL/min as estimated using Cockcroft-Gault formula	Calculated and documented by investigator in medical record based on Central Lab test report
4	Total bilirubin ≥ 34.2 μmol/L. [Patients with higher total bilirubin values may be included after the consultation with the Study Medical Monitor, if such elevation can be clearly attributed to Gilbert's syndrome associated with low-grade hyperbilirubinemia.]	Central Lab test report; Evidence of Gilbert's syndrome: anamnestic data (discharge) or assessed and documented by investigator in medical record
5	Evidence of an active or suspected malignancy or an untreated pre-malignancy disorder, or a history of malignancy within the last 5 years (with the exception of successfully treated carcinoma of the cervix in situ and successfully treated basal cell carcinoma and squamous cell carcinoma not less than 1 year prior to screening [and no more than 3 excised skin cancer within the last 5 years prior to screening]) or history of hepatic carcinoma	Assessed and documented by investigator in medical record
6	Systemic connective tissue disorders	Assessed and documented by investigator in medical record
7	New York Heart Association (NYHA) Class III-IV congestive heart failure	Assessed and documented by investigator in medical record
8	Patients with uncontrolled arterial hypertension: systolic blood pressure > 150 mm Hg and/ or diastolic blood pressure > 100 mm Hg at Screening.	Assessed and documented by investigator in medical record
9	Previous or unstable concurrent diseases or conditions that prevent subject's enrolment into the study	Assessed and documented by investigator in medical record

Exclusion Criteria		Confirmation
10	Patients with mental disorders or social circumstances that preclude them from following protocol requirements	Assessed and documented by investigator in medical record
11	Current or previous (within last 2 years) decompensated liver disease, including coagulopathy, hepatic encephalopathy and esophageal varices hemorrhage	Assessed and documented by investigator in medical record
12	One or more additional known primary or secondary causes of liver disease, other than hepatitis B (eg, alcoholism, autoimmune hepatitis, malignancy with hepatic involvement, hemochromatosis, alpha-1 antitrypsin deficiency, Wilson's Disease, other congenital or metabolic conditions affecting the liver, congestive heart failure or other severe cardiopulmonary disease, etc.). Gilbert's syndrome, a benign disorder associated with low-grade hyperbilirubinemia, will not exclude patients from participation in this trial. Autoimmune hepatitis stigmata attributed to HDV infection in the opinion of the investigator are allowed.	Assessed and documented by investigator in medical record
13	White blood cells (WBC) count < 3000 cells/mm^3 (< 1500 if African patients)	Central Lab test report
14	Neutrophil count < 1500 cells/mm^3 (<1000 if African patients)	Central Lab test report
15	Platelet count < 60,000 cells/mm^3	Central Lab test report
16	Use of prohibited psychotropic agents at Screening	Urine drug screening test result at site documented in medical record; Assessed and documented by investigator in medical record
17	Use of interferons within 6 months before Screening	Assessed and documented by investigator in medical record
18	History of solid organ transplantation	Assessed and documented by investigator in medical record
19	Current alcohol abuse or alcohol abuse within 6 months prior to enrolment in this study; past or current drug addict	Alco-test result at site documented in medical record; Assessed and documented by investigator in medical record

Exclusion Criteria		Confirmation
20	History of disease requiring regular use of systemic glucocorticosteroids (inhalative glucocorticosteroids are allowed) or other immunosuppressants	Assessed and documented by investigator in medical record
21	Pregnant or breast-feeding females	Pregnancy urine test result at site documented in medical record; Assessed and documented by investigator in medical record
22	Participation in another clinical study with investigational drug within 30 days prior to randomization	Assessed and documented by investigator in medical record
23	Receipt of bulevirtide previously, eg, in clinical trials	Assessed and documented by investigator in medical record
24	Inability to follow protocol requirements and undergo all protocol procedures. NOTE: Patients with medical contraindication for liver biopsy are allowed to participate in this study. Such patients will exempt from liver biopsy requirements in this study. Patients receiving prohibited treatment at Screening cannot be included into the study unless this treatment is withdrawn prior to randomization.	Assessed and documented by investigator in medical record

protocol MYR301 Amendment 4

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Clinical Research eSigned	28-Apr-2022 19:52:49