CLINICAL STUDY PROTOCOL

Study Title:	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
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Protocol Identification:	MYR204
Version Number and Date:	Version 5.0 dated 08-Feb-2022
EudraCT number:	2019-001485-15
ClinicalTrials.gov Identifier:	NCT03852433

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

SIGNATURE PAGE 1 (SPONSOR)

Protocol Title: 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.

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.

Signature: *[See appended electronic signature]* Date: *[See appended electronic signature]*

PPD

Medical Monitor, Clinical Development
Gilead Sciences, Inc.

_____/_____/_____
day/month/year

SIGNATURE PAGE 2 (PRINCIPAL INVESTIGATOR)

Protocol Title: 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.

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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Signature: _____

Date: _____

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LIST OF ABBREVIATIONS

AASLD	American Association for the Study of Liver Diseases
AE	Adverse event
AESI	Adverse Event of Special Interest
ADR	Adverse drug reaction
ALT	Alanine transaminase
aPTT	Activated partial thromboplastin time
AST	Aspartate transaminase
BID	Twice daily
BMI	Body mass index
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
CRF	Case report form
CRO	Contract research organisation
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
EASL	European Association for the Study of the Liver
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 glutamyl transferase
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HDV	Hepatitis delta virus
HIV	Human immunodeficiency virus
HPLC-MS	High performance liquid chromatography-mass spectrometry
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 Normalization Ratio
IRB	Institutional Review Board
LoD	Limit of detection
LLOQ	Lower limit of quantification
kPa	Kilopascal
MedDRA	Medical Dictionary for Regulatory Activities
mcg	Microgram
MMRM	Mixed effect repeated measurement models
NA	Nucleos(t)ide analogue
NCI	National Cancer Institute (USA)
NOCB	Next observation carried backward
NTCP	Sodium-taurocholate cotransporting polypeptide
OATP	Organic anion transporting polypeptide
PCR	Polymerase chain reaction
PEG-IFN alfa	Pegylated interferon alfa-2a
PI	Principal Investigator
PP	Per-protocol set
PT	Preferred Term
RBC	Red blood cell
QD	Once daily
REML	Restricted maximum likelihood
RNA	Ribonucleic acid
SAE	Serious adverse event
SC	Subcutaneously
SCR	Screening
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVR 24	Sustained virological response 24
SVR 48	Sustained virological response 48
TDF	Tenofovir disoproxil fumarate
TSH	Thyroid stimulating hormone (thyrotropic hormone)
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 2b Clinical Study to Assess Efficacy and Safety of Bulevirtide in Combination with Pegylated Interferon alfa-2a in Patients with Chronic Hepatitis Delta
Protocol Identification:	MYR204
Study sites:	Approximately 25 study sites in approximately 4 countries globally which may include Russia, France, Moldova, Romania
Phase of Development:	Phase 2b
Objectives:	**Primary:** The primary objective of this study is to evaluate the efficacy of bulevirtide administered subcutaneously at a dose of 2 mg or 10 mg in combination with pegylated interferon alfa-2a once weekly relative to 10 mg bulevirtide monotherapy in participants with chronic hepatitis delta. **Secondary:** • To assess the safety of bulevirtide. CCI [redacted]
Methodology:	This is a randomized, open label, active controlled, parallel group multicenter Phase 2b study that will evaluate the efficacy and safety of bulevirtide at daily doses of 2 and 10 mg in combination with pegylated interferon alfa-2a (PEG-IFN alfa) compared to monotherapy with bulevirtide at daily dose of 10 mg and monotherapy with PEG-IFN alfa-2a in participants with CHD.
Diagnosis and Main Criteria for Inclusion:	Adult male and female participants with chronic HDV infection, detectable HDV RNA and elevated ALT at Screening.
Treatments:	
Arm A:	Peginterferon alfa-2a for 48 weeks with additional 48 weeks follow-up
Arm B:	Bulevirtide 2 mg/day in combination with peginterferon alfa-2a for 48 weeks followed by bulevirtide 2 mg/day for 48 weeks and additional 48 weeks follow-up
Arm C:	Bulevirtide 10 mg/day in combination with peginterferon alfa-2a for 48 weeks followed by bulevirtide 10 mg/day for 48 weeks and additional 48 weeks follow-up
Arm D:	Bulevirtide 10 mg/day for 96 weeks with additional 48 weeks follow-up
Mode of Administration:	The study is open label. Treatments are administered as follows:

	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 subcutaneously (s.c.) daily, every 24±1 hours. **Bulevirtide 2 mg**: One injection of bulevirtide 2 mg. Injection is performed s.c. daily, every 24±1 hours. **PEG-IFN alfa:** One injection of PEG-IFN alfa 180 mcg. Injections are performed s.c. once a week.
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 practice guidelines (EASL and AASLD). The Sponsor will be providing tenofovir (tablets) if the drug cannot be made available for participants through routine medical care. In participants in whom tenofovir is contraindicated, entecavir (tablets) will be provided.
Criteria for Evaluation:	*Primary Efficacy Endpoint* Sustained virological response 24 (SVR 24) defined as undetectable HDV RNA (HDV RNA < limit of detection [LoD]) at week 24 after the scheduled end of treatment (follow-up week 24 [FU-24], i.e., study week 120 for Arms B, C and D). *Secondary Efficacy Endpoints* • Undetectable HDV RNA at week 48 (all arms), 96 (Arms B, C and D) • Combined sustained response at week 24 and 48 after the scheduled end of treatment where combined response is defined as fulfilment of two conditions simultaneously: - Undetectable HDV RNA or decrease by ≥ 2 $\log_{10}$ IU/mL from baseline. - ALT normalization • 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, 96, and 144 CCI [redacted]

Criteria for Evaluation (continued):	[redacted]) *Safety endpoints* • Frequency and nature of adverse events (based on assessments of clinical events, physical examination, vital signs, electrocardiogram 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 electrocardiogram • Changes in laboratory tests (hematology, coagulogram, biochemistry, blood bile salts, vitamin D) *Immunogenicity variables* • Appearance and concentration of bulevirtide antibodies *Pharmacokinetic variables* • Plasma concentration of bulevirtide *Other variables* • HDV/HBV genotyping • NTCP polymorphism • Resistance testing (HBV genotypic assay with focus on the HBV envelope, Phenotypic resistance assay and HDV genotypic assay) • HBeAg and HBeAg antibodies status at all postbaseline assessments (for participants 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)
Statistical Methods:	**Sample size** The primary efficacy analysis of this study is the estimation of the difference in rates between the combination of pegylated interferon + bulevirtide 10 mg (Arm C) and bulevirtide 10 mg monotherapy (Arm D) of sustained virological response (SVR 24) defined as undetectable HDV RNA at week 24 after the scheduled end of treatment i.e. at study week 120. With 48 participants per treatment group a two-sided continuity corrected 95%-confidence interval for the difference of the SVR 24 rates will extend less than 22.5% from the observed difference. The sample size will be slightly increased to 50 participants per treatment group to account for a few potential early withdrawals before exposure. The treatment group with the combination of pegylated interferon + bulevirtide 2 mg will be of the same size. The treatment group with the pegylated interferon will include 25 participants. Hence 175 participants will be randomized. **Analysis populations** • Enrolled set: All participants screened and enrolled (signed Informed Consent) into this study. • Randomized set: All enrolled and randomized participants. • Full analysis set (FAS): All participants randomized who received study medication (pegylated interferon and/or bulevirtide) at least once after randomization. • Per-protocol (PP) set: All participants of the FAS for whom no protocol deviations are judged to have an impact on the analysis of the primary efficacy endpoint of SVR24. Details will be specified in the statistical analysis plan and final decision on exclusion from PP set will be made in a data review meeting before data base lock. • Safety population: All participants who had been exposed to study medication (pegylated interferon and/or bulevirtide). Analyses based on the randomized set and the FAS will use the randomized treatment. Analyses based on the PP population and the Safety population will use the actual treatment received. **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 participants in the FAS and the PP population. Presentation for Safety, and Randomized set (if applicable) will be done if the corresponding set size differs from the FAS set size by more than 10%. **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

Statistical Methods (continued):	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 visit. Primary analysis The primary efficacy analysis of this study is the estimation of the difference in rates between the combination of pegylated interferon + bulevirtide 10 mg (Arm C) and bulevirtide 10 mg monotherapy (Arm D) of sustained virological response (SVR 24) defined as undetectable HDV RNA at week 24 after the scheduled end of treatment i.e. at study week 120. 95%-confidence interval with exact unconditional confidence limits using the score statistic will be presented for the rate differences. Clopper-Pearson 95%-confidence intervals will be calculated for the single rates. The p-value of a two-sided Fisher test will be calculated. Participants with missing FU-24 assessment in HDV RNA will be handled as non-responders unless it is related to coronavirus disease 2019 (COVID-19) in which case missing values will be imputed using the next observation carried backward (NOCB) approach. 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. The influence of covariables e.g. presence of cirrhosis and region will be investigated using logistic models. CCI 

Statistical Methods (continued):	**Analysis of safety** Adverse events Adverse events (AE) will be coded using MedDRA and will be presented by primary System Organ Class (SOC) and Preferred Term. The analysis will focus on the treatment-emergent AEs (TEAE), i.e., AEs which started or worsened after start of treatment and no later than 30 days after permanent discontinuation of treatment. The frequency of TEAEs will be summarized by incidences. In these summaries, each participant will be counted only once within each preferred term 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 dose reduction and AE 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). ECG 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 participants in each treatment group with QTc values 451 - 480 ms, 481 - 500 ms or >500 ms and the number and percent of participants in each treatment group who experienced a change vs. baseline >30 ms or a change >60 ms will be presented by visit. Immunogenicity The production of bulevirtide antibodies will be presented by visit. Pharmacokinetics Plasma concentration of bulevirtide will be described by descriptive statistics Other safety assessments Other safety variable will be described by appropriate descriptive statistics.

Table 1. Schedule of Events

Study phase	**Screening**	**48 (or 96)-week Treatment phase***		**48-week Follow-up phase***		
V (Visit) / W (Week) / D (Day)	**SCR**	**V1**	**V2 – V8**	**V9 – V14**	**FU 1**	**FU 2-5**	**FU 6 /EOS**
Procedures [1]	D-28 to D-1 **	W0 / D1	*±2 days* All groups: W4, W8, W16, W24, W32, W40, W48	*±2 days* **Only Arms B, C and D:** W52, W56, W64, W72, W84, W96	*± 3 days* A: W52 B, C, D: W100	*±3 days* A: W56, W64, W72, W84 B, C, D: W104, W112, W120, W132	*±7 days* A: W96 B, C, D: W144
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
Physical examination [5]	X	X [6]	X	X	X	X	X
Assessment of local reactions at the injection sites		X	X	X	X		
Complete eye examination	X		As clinically indicated				
Vital signs [7]	X	X	X	X	X	X	X
12-lead electrocardiogram (ECG)	X		X (W8, W24, W48)	X (W72, W96)		X (A: W72; B, C and D: W120)	X
Abdominal ultrasound	X						
Transient elastometry (Fibroscan)	X		X (W48)	X (W96)		X (A: W72; B, C and D: W120)	X
Breath alcohol test	X	X					
Inclusion/Exclusion criteria	X	X					
Adverse events (including liver related clinical events starting from the randomization)	X(SAE only)	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X

Study phase	**Screening**	**48 (or 96)-week Treatment phase***			**48-week Follow-up phase***		
V (Visit) / W (Week) / D (Day)	**SCR**	**V1**	**V2 – V8**	**V9 – V14**	**FU 1**	**FU 2-5**	**FU 6 /EOS**
Procedures [1]	D-28 to D-1 **	W0 / D1	*±2 days* All groups: W4, W8, W16, W24, W32, W40, W48	*±2 days* **Only Arms B, C and D:** W52, W56, W64, W72, W84, W96	*± 3 days* A: W52 B, C, D: W100	*±3 days* A: W56, W64, W72, W84 B, C, D: W104, W112, W120, W132	*±7 days* A: W96 B, C, D: W144
TREATMENT DISPENSING/RETURN							
Randomization [8]		X					
Study treatment dispensing [9]		X [9]	X [9]	X [9]			
Study treatment return and treatment compliance assessment			X	X			
Participant Diary Dispensing/Review/ Collection		X	X	X			
Quality of life questionnaires (EQ-5D, FSS, HQLQ™)		X	X (W24, W40, W48)	X (W72, W96)		X (W72)	X
LOCAL LABORATORY/STUDY SITE							
Urine pregnancy test [10]	X	X	X	X	X	X	X
Urine drug screening test	X						
ANALYSIS 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 [11]	X [11]	X	X	X
Hematology [12]	X	X [6]	X	X	X	X	X
Biochemistry (full panel) [13]	X	X [6]	X (W24, W48)	X (W72, W96)			X
Biochemistry (abbreviated panel) [14]			X (W4, W8, W16, W32, W40)	X (W52, W56, W64, W84)	X	X	
Coagulogram [15]	X	X [6]	X (W8, W24, W40, W48)	X (W64, W72, W84, W96)		X (W72, W120)	X
Total blood bile salts		X	X	X	X	X	X
Alpha-fetoprotein test	X						

Study phase	**Screening**	**48 (or 96)-week Treatment phase***			**48-week Follow-up phase***		
V (Visit) / W (Week) / D (Day)	**SCR**	**V1**	**V2 – V8**	**V9 – V14**	**FU 1**	**FU 2-5**	**FU 6 /EOS**
Procedures [1]	D-28 to D-1 **	W0 / D1	*±2 days* All groups: W4, W8, W16, W24, W32, W40, W48	*±2 days* **Only Arms B, C and D:** W52, W56, W64, W72, W84, W96	*± 3 days* A: W52 B, C, D: W100	*±3 days* A: W56, W64, W72, W84 B, C, D: W104, W112, W120, W132	*±7 days* A: W96 B, C, D: W144
Vitamin D		X	X (W24, W48)	X (W72, W96)		X (W72, W120)	X
TSH[16]	X		X (W8, W24, W48)				
Serum alpha-2-macroglobulin		X	X (W48)	X (W96)		X (W120)	X
HBV DNA for pts. not receiving Nucleoside / nucleotide analogues	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							
HDV genotyping		X					
HDV RNA		X	X	X	X	X	X
HBV DNA (HBV genotyping at first positive HBV DNA)		X	X	X	X	X	X
HBsAg		X	X	X	X	X	X
HBsAg antibodies [17]		X	X (W24, W48)	X (W72, W96)		X (A: W72; B, C and D: W120)	X
HBeAg and HBeAg antibodies [18]		X	X (W48)	X (W96)			X
ANALYSIS PERFORMED IN CENTRAL LABORATORY / SAMPLES TO BE STORED AT SITE							
Immunogenicity (bulevirtide antibodies) [19]		X	X (B, C and D: W16, W24, W48)	X (W72, W96)		X (B, C and D: W120)	X
NTCP polymorphism[20]		X					
Resistance tests (HBV genome sequencing, Phenotypic assay, HDV genome sequencing) [21]		X[21]	X [21]	X [21]	X [21]	X [21]	X [21]
Pharmacokinetics [22]		X [22]	X [22]	X[22]			
Liver biopsy	X [23]					X (A: W72; B, C, and D: W120) [24]	

EQ-5D – EuroQol 5-Dimentions; FSS – Fatigue Severity Scale; HQLQ™ – The Hepatitis Quality of Life Questionnaire™.

* Duration of treatment is 48 weeks for Arm A and 96 weeks for Arms B, C and D. For participants of Arm A the Follow-up period starts after W48 of treatment. For participants of Arms B, C and D the Follow-up period starts after W96 of treatment. See study design for detailed information on duration of treatment in different groups.
**Screening can be shorter than 28 days as soon as eligibility of participant 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 includes: 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 participant 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. Vital signs include body temperature, heart rate and blood pressure. Vital signs are measured as indicated in Table 1 and when clinically indicated.
8. Participants eligible for the study are randomized after completion of all procedures scheduled for Screening and Day 1 related to confirmation of participant's eligibility (See Section 4). All other procedures of Day 1 (except sample collection for pharmacokinetic and assessment of adverse events including assessment of injection site reaction) should be performed before study drug administration.
9. Participants 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 immunogenicity and pharmacokinetics of the study drug.
10. Only for women of childbearing potential.
11. Urinalysis is not needed at W4, W52 (for B, C and D arms only. Assessment for Arm A at FU1 is required).
12. Hematology includes: hemoglobin, hematocrit, reticulocytes, RBC, platelet count, WBC with differential (absolute counts and percentage for neutrophils, eosinophils, basophils, monocytes, and lymphocytes).
13. Full biochemistry (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).
14. Abbreviated biochemistry (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).
15. Coagulogram includes prothrombin time, INR and aPTT.
16. Only for Arms A, B, C
17. Collection of anti-HBsAg samples at designated time points; testing only if HBsAg becomes undetectable.
18. Collection and testing of HBeAg and HBeAg antibodies only if participant is HBeAg positive at SCR.

19. Samples for immunogenicity assessment should be taken before administration of the study drug(s), for B, C and D arms only.
20. Blood samples for determination of NTCP polymorphism are collected at Day 1 for all the participants. NTCP polymorphism will be performed in central laboratory for participant 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 participants 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. Pharmacokinetics samples are taken only for Arms B, C and D. 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 participant 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 participant 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 participants 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 D virus (HDV), which requires the presence of 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. 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. Eight genotypes of HDV exist, whereas genotype 1 is the most common in the world and in Europe (2).

In general, HDV is a highly pathogenic virus causing acute and chronic liver disease. Although benign course of the disease has been described (3), patients with hepatitis delta 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 (4,5). 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 (6). There is no histological feature distinctive of hepatitis delta from other types of viral hepatitis. Biopsy specimens of patients with chronic hepatitis delta exhibit portal and periportal inflammation, fragmentary necrosis, often accompanied by fibrosis and cirrhosis. Marked intraglobular infiltration by mononuclear cells and degenerative changes in hepatocytes is seen (7). Clinically, hepatitis delta 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 (CHD) 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 (8). Hepatitis delta is considered the most severe form of viral hepatitis in humans (9), and is associated with progression of liver disease, development of cirrhosis and decompensation (10,11).

CCI [redacted] In regions endemic for HDV infection, the liver disease is representing a major health care challenge. A study from Italy has shown existence of HDV antibodies in as many as 40% of patients with liver cirrhosis in 1987. Although this number has declined to 11% in 2000 (13), the HDV-caused disease is still a significant burden. A longitudinal study has shown that 20% of hepatitis delta patients develop a liver-related first time event during the median follow-up time of 4 years, vs only 8.5% of HBV monoinfected patients (14). 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 (15). HDV co-infection is associated with faster progression to fibrosis and cirrhosis, earlier onset of hepatic complications and likelihood of liver transplantation (3,16,17). 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 (18). Chronic HDV infection causes cirrhosis and hepatocellular carcinoma (HCC) with annual rates of 4% and 2.8%, respectively (15).

In average, 5-10% of HBsAg-positive patients who admit to tertiary centers are tested positive for HDV in the EU. The calculation of total number of people affected by hepatitis delta in the EU has yielded the estimate of 145,000 persons. Accounting for EU population of 505,665,700 (2013), the prevalence of the condition is estimated to be 2.9 in 10,000 people which is below the Orphan Drug designation threshold.

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 (19). 11% of injection drug users were tested positive for HDV in Baltimore; in those with chronic HBV infection, 50% were HDV positive (20). In 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 hepatitis delta 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 limited. Previously, only interferons show some degree of efficacy in a small proportion of patients with approximately 25% of virological and biochemical response. Antiviral agents active against HBV do not work against HDV (17).

Several clinical trials were recently performed investigating the use of pegylated interferon alpha in hepatitis delta. The two large trials in this indication, HIDIT-1 and HIDIT-2, did show only very modest long-term virological results. In the HIDIT-1 clinical trial, pegylated interferon was tested in combination with nucleotide analogue adefovir dipivoxil versus either drug along in 91 chronically HDV infected participants (21). At test week 48, 23% of participants on combination therapy, 24% on pegylated interferon monotherapy, and no participants on adefovir reached HDV RNA negativation. The effect was sustained through week 24. However, the follow-up study revealed that from 16 individuals who have reached HDV RNA negativity at the end of treatment, 9 tested positive within the median follow-up of 4.5 years (0.5-5.5 years) (22). In the HIDIT-2 clinical trial, 120 participants received pegylated interferon alpha with or without tenofovir disoproxil fumarate for 96 weeks. The prolongation of the interferon treatment to 96 weeks and addition of nucleotide analogue Tenofovir did not improve sustained virological response rates: 30% of participants in the combination arm and 23% of participants in the monotherapy arm were HDV RNA negative 24 weeks after the end of treatment. Of note, 20 participants (16%) did not complete at least week 80 of treatment. A trial involving 49 participants treated with pegylated interferon alpha 2b has shown 33% of HDV RNA negativation at the end of treatment (48 weeks) and 25% at the end of follow-up (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.

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 European Union (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 one clinical study is 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 participants 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 participants 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 participants 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 participants with chronic hepatitis B with delta-agent (Russia) *[completed]*

- 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 I single-dose study (MYR101) was conducted in 36 healthy male participants. 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 participants. 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 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 two were severe (Grade 3) according to CTCAE 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 participants, no 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 participants investigated the influence of receptor-saturating dose on pharmacokinetics of anti-HBV drug tenofovir. Twelve healthy participants received 245 mg of oral tenofovir disoproxil 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 CYP3A activity.

The combination of bulevirtide and tenofovir was well tolerated. A total of 28 adverse events 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 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 adverse events were mild. Lipase levels showed marked day to day fluctuations in this participant. Two participants 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 pharmacokinetics including renal tenofovir clearance. 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 tenofovir 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 tenofovir, and 724.8 mL/min (592.5, 886.7; p-value 0.02 vs. baseline) under tenofovir and bulevirtide treatment.

Differences were significant between baseline and co-administration of tenofovir and bulevirtide, but not between tenofovir 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 tenofovir or its prodrug might account for the statistically inconclusive results. Coadministration of regular tenofovir 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.

MYR201 Study (Part I – Chronic Hepatitis B)

This was an CCI randomized, open-label, multicenter, active-controlled, parallel-group study of daily bulevirtide versus Entecavir in participants with HBeAg negative chronic hepatitis B. Participants of both sexes at the age of 18–65 years with HBeAg negative chronic hepatitis B and mild to moderate disease activity confirmed by HBV DNA ≥ 10 000 copies/mL and ALT level ≥ 1.5 × ULN and ≤ 6 x ULN were enrolled into this study. A total of 48 participants were randomized into 6 treatment groups, each of 8 participants:

Cohort A (n=8): Bulevirtide 0.5 mg daily subcutaneously (SC) for 12 weeks + 12 weeks follow-up

Cohort B (n=8): Bulevirtide 1 mg daily SC for 12 weeks + 12 weeks follow-up

Cohort C (n=8): Bulevirtide 2 mg daily SC for 12 weeks + 12 weeks follow-up

Cohort D (n=8): Entecavir 0.5 mg daily orally for 24 weeks

Cohort E (n=8): Bulevirtide 5 mg daily SC for 12 weeks + 12 weeks follow-up

Cohort F (n=8): Bulevirtide 10 mg daily SC for 24 weeks + 12 weeks follow-up

Safety and tolerability, plasma pharmacokinetic parameters, immunogenicity and virological responses were assessed in this trial. Levels of HBsAg, HBV DNA and ALT were used to assess efficacy.

A dose-dependent decrease in viral load was reported at week 12 of treatment. Six (6) of 8 participants (75%) of the 10 mg bulevirtide cohort had a decline in serum HBV DNA of more than 1 $\log_{10}$ IU/mL in comparison to baseline. The participants of the 10 mg bulevirtide cohort continued the treatment for 24 weeks, maintaining HBV DNA levels achieved at week 12. At lower dose levels, no per cohort dose dependency was observed; per cohort, at most 25% of lower dose participants achieved > 1 $\log_{10}$ IU/mL HBV DNA reduction at week 12. Normal ALT was reported in 50-75% of participants receiving bulevirtide at week 12, irrespective of dose level. No effect on HBsAg was observed.

A total of 69 adverse events were reported during the study. Overall, in the bulevirtide treatment groups the AEs were predominantly clustered in the same 4 SOCs: 'General disorders and administration site condition'; 'Investigations'; 'Skin and subcutaneous tissues disorders'; 'Blood and lymphatic system disorders'. In the Entecavir treatment group all the AEs were in the 3 SOCs: 'General disorders and administration site condition'; 'Infections and infestations'; 'Respiratory, thoracic and mediastinal disorders'.

A total of 45 adverse events were considered as related with bulevirtide. In general, treatment-related AEs were of mild severity (a total of 41 events). The events of moderate severity were erythema, gamma-glutamyltransferase increased, reticulocyte increased, injection site dermatitis. Neither treatment group had any reports of AEs judged to be severe. There were 2 AEs considered to be serious: drug withdrawal syndrome reported for 1 participant of the 1 mg bulevirtide cohort and 1 participant of the 2 mg bulevirtide cohort. There were no participants who prematurely discontinued participation in the study due to AE/SAE. There were no deaths in the study.

Levels of bile salts are important secondary pharmacodynamics parameter, as a bile salts transporter NTCP is the target of bulevirtide. A dose-dependent, asymptomatic increase of bile salts which are NTCP substrates (i.e. taurocholate and glycocholate) was detected; whereas lithocholic acid (non-substrate for NTCP) levels were not affected. Antibodies to bulevirtide were detected in 58% of participants of bulevirtide dose groups. No correlation was observed between the appearance of antibodies and pharmacodynamic parameters. Elevated levels of bile salts, which are a secondary pharmacodynamic parameter and are indicative for drug-target binding, were detected independent of antibody positivity. Virological and biochemical response was not different in participants who were antibody-positive versus antibody-negative.

MYR201 Study (Part II – Chronic Hepatitis Delta)

This was a randomized, open-label, single-center, active-controlled, parallel-group study. Participants of both sexes at the age of 18–65 years with HBV/HDV co-infection confirmed by the presence of HBsAg for at least 6 months and positive 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 participants were randomized in 1:1:1 ratio into the 3 treatment arms:

Arm A (n=8): Bulevirtide 2 mg daily subcutaneous injection (SC) for 24 weeks, followed by PEG IFN alfa-2a for 48 weeks + 24 weeks follow-up

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

Arm C (n=8): PEG IFN alfa-2a for 48 weeks + 24 weeks follow-up

Safety and tolerability, immunogenicity 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 PEG IFN alfa-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 participants). Overall, both bulevirtide-containing regimens (Arm A and B) showed more considerable HBV DNA response as compared with PEG IFN alfa-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 (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 participants treated with PEG IFN alfa-2a (6/7 participants). The combination treatment of bulevirtide + PEG IFN alfa-2a demonstrated the highest response rate, thus indicating a potential synergistic effect (7/8 participants). HDV RNA became undetectable in 2 of 7 participants treated with bulevirtide (Arm A) and PEG IFN alfa-2a (Arm C) and in 5 of 8 participants treated with bulevirtide + PEG IFN alfa-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 PEG IFN alfa-2a led to the decrease of ALT response. No considerable difference was observed between Arm B and Arm C.

All randomized participants (24/24, 100.0%) experienced at least one 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 with the most AEs reported were leucopenia, neutropenia, thrombocytopenia, each reported in more than 5 participants 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 participants) as compared with Arm B and C (3 participants). Influenza-like illness was the most reported adverse event within the SOC “General disorders and administration site conditions”.

The majority of AEs were of mild or moderate in intensity. A few participants experienced severe AEs during the study: 1 participant in Arm B and 2 participants 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 participants) of the PEG IFN-alpha 2a-related AEs in each treatment group, while the incidence of the bulevirtide-related AEs comprised 37.5% (3 participants) in Arm A and 12.5% (1 participant) in Arm B. Those related to PEG IFN-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 participant discontinued the study due to AE: participant from Arm B who experienced rash of moderate intensity that was judged to be related to PEG IFN-alpha 2a.

There was on-treatment immune response observed for both bulevirtide-containing regimens (Arm A and B). Overall, there were 4 participants in Arm A and 7 participants in Arm B that had positive immunogenicity response (increase of bulevirtide antibodies by >2 fold as compared to baseline). After the cessation of bulevirtide, there was a significant decline of anti-drug antibodies titers. There were no obvious signs of the influence of immunogenicity on safety and efficacy results found in Arm A and B.

MYR202 Study (Completed)

MYR202 study aimed to evaluate the efficacy and safety of bulevirtide at daily doses of 2, 5 or 10 mg in combination with tenofovir disoproxil fumarate (TDF) compared to TDF alone in participants with chronic hepatitis D.

The primary efficacy endpoint was HDV RNA response at week 24 defined as undetectable HDV RNA or 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 participants with HDV RNA response and combined response at week 24 is shown in Table 2. There was significantly higher percentage of participants with HDV RNA response at week 24 in all bulevirtide groups compared to TDF group ($p<0.0001$ for all bulevirtide groups).

Table 2. Participants with HDV RNA response and combined response at week 24 (MYR202 study, mITT population)

	Bulevirtide 2 mg + TDF (N=28)	Bulevirtide 5 mg + TDF (N=32)	Bulevirtide 10 mg + TDF (N=30)	TDF (N=28)
Participants with HDV RNA response at week 24, n (%)	**15 (53.6)***	**15 (46.9)***	**24 (80.0)***	**1 (3.6)**

Participants 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: 32

MYR203 Study (Completed)

MYR203 study 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 a daily dose of 5 mg BID in combination with TDF compared to pegylated interferon alone, in participants with chronic hepatitis D.

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 BID) + TDF

The primary efficacy endpoint was defined as the proportion of participants with a negative 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 BID + 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 BLV treatment groups and the delayed treatment group were as follows; the differences were statistically significant for both BLV 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%; $p < 0.0001$)

Refer to the bulevirtide Investigator's Brochure for details on nonclinical and clinical studies.

1.4. Study Rationale

There is currently no approved drug for treatment of CHD. Pegylated interferon alfa -2a (PEG-IFN alfa) is approved for treatment of chronic HBV infection which is required for the propagation of HDV, and used to treat participants with HDV infection with evidence of some virologic efficacy (21-23). Interferon has a complex mode of action, whereas direct antiviral

effects and immunomodulatory mechanisms have been described. Bulevirtide is an entry inhibitor has demonstrated significant virologic and biochemical activity in participants with HDV infection during the Phase 2 clinical trials. A combination of the both drugs demonstrated significant synergistic effects in the 201 clinical trial. It is therefore warranted to further investigate the combination therapy with the aim of improvement of sustained virologic response rates.

Graphic representation of the study design is shown in Figure 1.

1.4.1. Rationale for Participant Population

In participants 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 participants with HDV infection resulted in a significant 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. Participants 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.

Participants with ALT ≥ 10 × upper limit of normal (ULN), creatinine clearance < 60 mL/min, total bilirubin ≥ 34.2 µmol/L, HCV or HIV coinfection, hepatocellular carcinoma, decompensated liver disease, 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

The dose of 10 mg was selected for monotherapy and for the combination arm with PEG-IFN as this dose has demonstrated the highest HDV virologic response rates in the 202 clinical trial. The 2 mg dose in combination with PEG-IFN demonstrated synergistic effects in 201 study. The PEG-IFN monotherapy cohort will be added as a mode of action / effect contribution arm.

In order to further increase SVR rates in this difficult to treat indication, the "tale" of 48 weeks of bulevirtide therapy will be introduced after the completion of 48 weeks combination.

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, immunogenicity, 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 risks associated with pegylated interferon treatment are generally mild, not treatment-limiting and well-established. The most common side effects include fatigue, fever, headache, injection-site reactions, rigors, myalgia, arthralgia, nausea, weight decrease, anorexia, depression, insomnia, irritability, alopecia, rash, dry skin. Influenza-like symptoms are common and develop more often in patients who are using high doses of pegylated interferon (28). These data are in alignment with the results obtained by Janssen et al (2005). They have also established that the most common side-effects associated with pegylated interferon treatment are flu-like symptoms, headache, fatigue, and local reaction at the injection site (29).

The design of this study contains adequate measures to mitigate risk factors and adequate safety monitoring to protect the participants. 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 coronavirus disease 2019 (COVID-19) pandemic spread in the world, e.g. for participants 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 Chronic Hepatitis Delta, 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 participants.

The investigators, in coordination with the Sponsor, should assess the risks of any changes considered in the trial for each single participant and each single procedure with regard to the safety of the participant and the integrity of the trial data, with priority given to the safety of the participant. 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 at a dose of 2 mg or 10 mg in combination with pegylated interferon once weekly relative to 10 mg bulevirtide monotherapy in participants with chronic hepatitis delta.

Secondary objectives:

- To assess the safety of bulevirtide.

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2.2. Endpoints

Primary efficacy endpoint:

Sustained virological response 24 (SVR 24) defined as undetectable HDV RNA (HDV RNA < LoD) at week 24 after the scheduled end of treatment (follow-up week 24 [FU-24], i.e., study week 120 for Arms B, C and D).

Secondary efficacy endpoints:

- Undetectable HDV RNA at week 48 (all arms), 96 (Arms B, C and D).
- Combined sustained response at week 24 and 48 after the scheduled end of treatment where combined response is defined as fulfilment of two conditions simultaneously:
  - Undetectable HDV RNA or decrease by ≥ 2 $\log_{10}$ IU/mL from baseline.
  - ALT normalization
- 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, 96, and 144.

CCI

[redacted]

Safety endpoints:

- Frequency and nature of adverse events (based on assessments of clinical events, physical examination, vital signs, electrocardiogram 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 electrocardiogram
- Changes in laboratory tests (hematology, coagulogram, biochemistry, blood bile salts, vitamin D)

Immunogenicity variables:

- Appearance and concentration of bulevirtide antibodies

Pharmacokinetic variables:

- Plasma concentration of bulevirtide

Other variables:

- HDV/HBV genotyping
- NTCP polymorphism
- Resistance testing (HBV genotypic assay with focus on the HBV envelope, Phenotypic resistance assay and HDV genotypic assay)
- HBeAg and HBeAg antibodies status at all postbaseline assessments (for participants 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, active-controlled, parallel-group multicenter Phase 2b study that will evaluate the efficacy and safety of bulevirtide at daily doses of 2 and 10 mg in combination with PEG-IFN alfa-2a compared to monotherapy with bulevirtide at daily dose of 10 mg in participants with CHD.

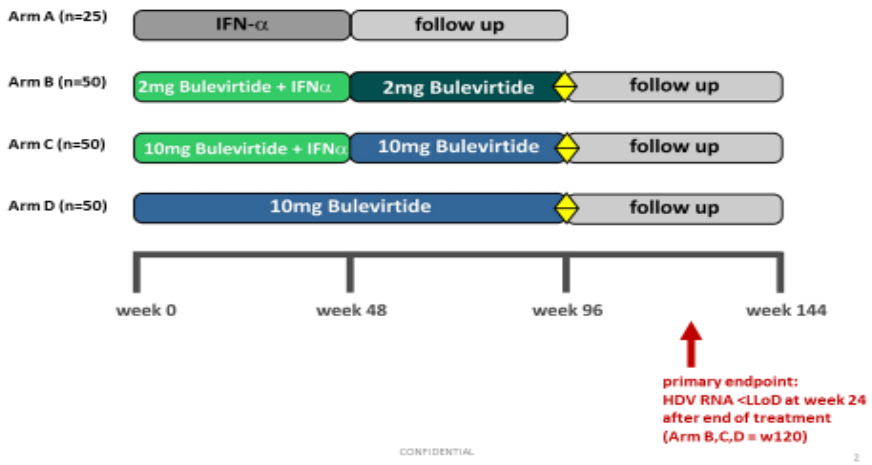
This study will be conducted at approximately 25 sites across approximately 4 countries globally which may include Russia, France, Moldova, Romania. A total of 175 participants will be randomized.

Participants will be assessed for eligibility to enter the study during a 4-week Screening period. Eligible participants will be randomized at Visit 1 in a 1:2:2:2 ratio with stratification for the presence of liver cirrhosis (no/yes) to receive PEG-IFN alfa-2a (Arm A), combination of PEG-IFN alfa-2a with bulevirtide 2 mg/day (Arm B), combination of PEG-IFN alfa-2a with bulevirtide 10 mg/day (Arm C) or bulevirtide 10 mg/day (Arm D) respectively.

At week 48 all participants that received PEG-IFN alfa-2a (Arms A, B and C) discontinue its use. Participants in Arm A are followed for additional 48 weeks. Participants in Arms B, C and D continue treatment with bulevirtide at initially assigned dose until week 96 and they are followed until week 144 (See Figure 1).

The total duration of treatment period is 48 weeks for Arm A and 96 weeks for Arms B, C and D. After completion of the treatment period, participants are followed for additional 48 weeks. The total amount of time to complete the study is 96-100 weeks (inclusive of the Screening, Treatment, and Follow-Up Periods) for Arm A and 144-148 weeks for Arms B, C and D. A scheme of the study design is presented in Figure 1. The schedule of events to be conducted during the Treatment Period and the 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



The study will be considered to have started when the first participant has provided signed informed consent, and will be considered to have finished after the last participant has completed the last follow-up visit.

3.1. Randomization

Participants eligible for the study are randomized after completion of all procedures scheduled for Screening and Day 1 related to confirmation of participant's eligibility (See Section 4). All other procedures of Day 1 (except sample collection for pharmacokinetic and assessment of adverse events including assessment of injection site reaction; See Table 1) should be performed before study drug administration.

Participants 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 participants 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 1:2:2:2 allocation ratio with stratification for the presence of liver cirrhosis (no/yes); each participant will be assigned a unique randomization code.

3.2. Blinding

This is an open label study for study participants and investigators at study sites. Central laboratories (except the laboratories for pharmacokinetic, immunogenicity, 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 participants will be enrolled at approximately 25 study sites across approximately 4 countries. A total of 175 participants will be randomized. Enrolment will stop as soon as the target number of randomized participants is reached.

Before randomization of study participant eligibility must be confirmed by the Medical Monitor. Investigator should record all relevant information about the study participant 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 participant's eligibility.

The laboratory results from Day 1 are not supposed to be used for participant'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.

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

3) Positive serum 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) Alanine transaminase level >1 × ULN, but less than 10 × ULN.

6) Serum albumin >28 g/L.

7) Thyroid stimulating hormone (TSH) within normal ranges (including on medication for control of thyroid function)

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

9) Inclusion criteria for female participants:

    a) Postmenopausal for at least 2 years, or

b) Surgically sterile (total hysterectomy or bilateral oophorectomy, bilateral tubal ligation, staples, or another type of sterilization), or

c) Abstinence from heterosexual intercourse throughout the treatment period, or

d) Willingness to use highly effective contraception (double barrier method or barrier contraception in combination with hormonal or intrauterine contraceptive) throughout the treatment period and for 6 months after the last dose of the study medication.

10) Male participants 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 treatment period and for 6 months after the last dose of the study medication.

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 of B-C or over 6 points. NOTE: Child-Pugh hepatic insufficiency score of 6 points is allowed. Only participants with compensated cirrhosis are allowed. Uncomplicated oesophageal varices allowed; Participants with current bleeding or ligation, or history of bleeding or ligation within the last 2 years are excluded.

2) HCV or HIV coinfection. Participants with HCV antibodies can be enrolled, if screening HCV RNA test is negative.

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

4) Total bilirubin ≥ 34.2 μmol/L. [Participants 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 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.

6) Systemic connective tissue disorders.

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

8) Participants 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 participant's enrolment into the study.

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

11) Current or previous 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 (e.g., 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 participants 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 participants).

14) Absolute neutrophil count < 1500 cells/mm^3 (<1000 if African participants).

15) Platelet count < 90,000 cells/mm^3.

16) Hemoglobin < 12 g/dL.

17) Use of prohibited psychotropic agents at Screening.

18) Use of interferons within 6 months before Screening.

19) History of solid organ transplantation.

20) Current alcohol abuse or alcohol abuse within 6 months prior to enrolment in this study; current drug addict or history of drug use within 2 years prior to Screening.

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

22) Pregnant or breast-feeding females.

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

24) Receipt of bulevirtide previously, e.g. in clinical trials.

25) Inability to follow protocol requirements and undergo all protocol procedures. NOTE: Participants with medical contraindication for liver biopsy are allowed to participate in this study. Such participants will exempt from liver biopsy requirements in this study.

26) Participants receiving prohibited treatment at Screening cannot be included into the study unless this treatment is withdrawn prior to randomization.

27) Contraindications, intolerance or hypersensitivity to interferons alfa, genetically engineered E.coli medications, polyethylene glycol or other components of peginterferon alfa-2a.

28) Presence or history of severe retinopathy, significant diabetic or hypertensive retinopathy.

29) Uncontrolled diabetes mellitus.

30) Uncontrolled cardiovascular disorders within 6 months before screening.

31) History of autoimmune disorder (e.g. myositis, hepatitis, thrombotic thrombocytopenic purpura, idiopathic thrombocytopenic purpura, severe psoriasis, rheumatoid arthritis, interstitial nephritis, thyroiditis, and systemic lupus erythematosus)

32) Presence or history of significant psychiatric disorder (e.g. severe depression, suicide attempt, severe neurosis or cognitive disorder).

33) Presence or history of chronic lung disease with respiratory malfunction.

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 participant's decision to withdraw and enter them into eCRF.

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

1) Informed consent withdrawal by the participant.

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

3) Investigator decides to withdraw the study participant 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 participant'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 participant from the study.

8) Pregnancy during the study.

9) Participant is lost to follow-up.

Investigator is responsible for obtaining and documenting the reason(s) for participant's withdrawal from the study after randomization and entering all relevant information into eCRF, including detailed information about the reason for the participant's withdrawal from the study when participants agrees to provide such information. If the participant 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 participants to the Sponsor and the Clinical research associate (CRA) within 24 hours.

4.4. Replacement of Participants

Study participants 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 participants 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: 2 R injection vial, colorless glass, European Pharmacopoeia (Ph. Eur.) Hydrolytic class I.

Closure: Lyophilization rubber stopper for 2R vials, Ph. Eur. 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 participants to store the drug at +2-8°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.

5.1.2. Peginterferon Alfa-2a

Drug formulation: Solution for subcutaneous administration.

Composition

Active ingredient: Peginterferon alfa-2a 180 mcg/0.5 mL.

Excipients: acetic acid, benzyl alcohol, polysorbate 80, sodium acetate, sodium chloride, and water for injection.

Appearance: Colorless to slightly yellowish solution.

Packaging

Peginterferon alfa-2a will be supplied in commercially available package.

Storage

Refer to package insert for information on storage of Peginterferon alfa-2a.

5.2. Labelling of Bulevirtide and Peginterferon Alfa-2a

Labelling of packages of the study products, 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 Participants with Bulevirtide and Peginterferon Alfa-2a

Investigator or designated person is responsible for supplying participant with the study drugs (bulevirtide and Peginterferon alfa-2a).

Participants 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

Participants 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 participant to visit the site for drug(s) supplying, upon consent of the participants and by the decision of investigator, the drug(s) may be delivered to the participant.

5.3.2. Administration of Bulevirtide

Bulevirtide is administered by study participants 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. Participants should be instructed NOT to administer bulevirtide 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 immunogenicity and pharmacokinetics of the study drug (i.e. sample for immunogenicity assessment is taken before administration of bulevirtide and sample for pharmacokinetics is taken 1h±15 min post bulevirtide dose).

Study site staff will instruct participants on procedures for storage, preparation and subcutaneous administration of the study drugs. Instructions for participants will be provided within the participant diary.

Participants randomized to receive bulevirtide at 2 mg daily dose administer bulevirtide by 1 subcutaneous injection. Participants randomized to receive bulevirtide at 10 mg daily dose administer bulevirtide by 2 subcutaneous injections (5 mg of bulevirtide twice). For participants 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.

Participant 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 ±1 hour. Deviation ±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 self-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.

5.3.3. Administration of Peginterferon Alfa-2a

Peginterferon alfa-2a is administered at a dose 180 mcg. Injections are performed SC once a week for 48 weeks. Peginterferon alfa-2a should follow the rules described in current approved version of label text/prescription information for Peginterferon alfa-2a.

Peginterferon alfa-2a is administered in outpatient setting.

At days of simultaneous administration of peginterferon alfa-2a and bulevirtide, bulevirtide should be administered first and Peginterferon alfa-2a should be administered after bulevirtide. If bulevirtide is delayed due to the visit to the study site Peginterferon alfa-2a should be also delayed.

SC injections of Peginterferon alfa-2a and bulevirtide are performed at different anatomical regions.

5.3.4. Dose Adjustment Guidelines

It is possible that some participants will encounter transient or prolonged adverse effects during their participation in the trial engendering the need to adjust test drug dosage. To minimize the effects of these modifications on the evaluation of the safety, tolerability, and efficacy of test drug regimens, the principles in the following sections will be used to adjust the dose of test drugs.

Treatment Interruption

If missing of one several doses of bulevirtide or PEG-IFN alfa is considered necessary to manage adverse events, such cases should be promptly discussed with the Sponsor.

If treatment interruption or permanent withdrawal of either bulevirtide or PEG-IFN is considered for participants receiving combination of these drugs, such cases should be promptly discussed with the Sponsor. Treatment with bulevirtide as monotherapy can be continued according to the scheduled regimen if participant’s condition allows continued participation in this study.

5.3.5. Dose Adjustment Guidelines for Bulevirtide

General Aspects

If Investigator believes that the participant 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 participant’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 participant 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 Participant Diary and case report form (CRF).

Treatment Adherence

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

5.3.6. Dose Adjustment Guidelines for Peginterferon Alfa-2a

Dose Adjustment Guidelines for Peginterferon Alfa-2a due to Intolerance

If in the opinion of the Investigator the treatment with Peginterferon alfa-2a should be suspended or prematurely terminated due to intolerance, the participant can continue his participation in the study.

Follow information provided in current approved version of label text/prescription information for instructions on dose adjustment of Peginterferon alfa-2a due to AEs.

Once the participant's unit dose has been decreased, the investigator may attempt to increase the dose back to or toward that which was originally assigned only if the event or circumstance responsible for the dosage adjustment has resolved or improved.

If four or more consecutive doses of Peginterferon alfa-2a are held or otherwise not administered (i.e., the participant has not received test medication for more than 28 days), the participant will be considered intolerant of the test medication or non-compliant, whichever is more appropriate to the clinical situation. No additional test drug may be administered to such participants without explicit permission from the sponsor.

Missing doses and Missed doses

If consistent with participant safety, doses should not be held or eliminated. This recommendation stems from concerns that extended periods of lowered drug concentrations in the blood may be associated with the replication of the more resistant clones of the virus, resulting in a lack of sustained response at the conclusion of therapy.

When the investigator considers it prudent to hold a dose, consideration needs to be given to informing the sponsor of the missed scheduled dose and the reasons the dose was withheld. Investigators should consider if adjusting the dose, either transiently or permanently, might be appropriate rather than holding a dose.

If a Peginterferon alfa-2a dose is delayed but eventually administered, the following guidelines should be utilized for the next scheduled dose(s):

Dose delayed 1 or 2 days:	Administer on usual dosing day of the week (e.g., if Monday is the usual dosing day and the dose is delayed until Wednesday, the next dose may be administered as usual on Monday).
Dose delayed 3-5 days:	Administer subsequent doses every 5th or 6th day until the participant is back to his or her original schedule (e.g., if Monday is the usual dosing day and the dose is delayed until Saturday, the next dose should be administered on Thursday, the following dose on Tuesday, then the dose after that as usual on Monday).
Dose delayed 6 days:	Hold the dose for that week then continue on the usual schedule the following week (e.g., if Monday is the usual dosing day but the participant is not ready to be dosed until the following Sunday, the dose is considered to have been held and the next injection should be for the following week's dose on Monday).
Dose delayed ≥7 days:	The investigator may reintroduce test drug at any time and, if necessary, dose the participant every 5th or 6th day until the participant resumes weekly dosing on their usual scheduled day.

5.3.7. Dose Adjustment Guidelines for Peginterferon Alfa-2a in Case of ALT Increases

Participants experiencing ALT flares (e.g. progressive ALT elevations of >10 × ULN) should receive more frequent monitoring of liver function until the ALT levels are stabilized. PEG-IFN alfa dose should be reduced in participants experiencing progressive or clinically significant ALT increase. If ALT increases are progressive despite reduction of PEG-IFN alfa dose or are accompanied by increased bilirubin or evidence of hepatic decompensation (i.e. hypoalbuminemia, increases in coagulation times), PEG-IFN alfa should be immediately discontinued.

5.4. 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 participant, batch and participant numbers must be kept.

5.5. Treatment Compliance

Both participant's diary information and drug accountability information will be used to estimate treatment compliance. Information about each study drug administration (i.e. time of administration and administered dose) will be captured in participant's diary by participant. All empty vials and syringes of the study drugs and unused drugs are returned by participant to investigator at each visit. Participant's diary information and drug accountability information (i.e. number of dispensed vials and/ or syringes with the study drug and the number of returned empty vials and/ or syringes of the study drugs) is entered in eCRF at each visit of participant to study site.

5.6. 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.

5.6.1. Treatment With Nucleoside/Nucleotide Analogues

The following rules should be followed:

1) Participants who receive the treatment with nucleoside/nucleotide analogue (NA) for chronic HBV infection at screening will continue their treatment as prescribed.

2) For participants not on NA treatment at screening, such treatment should be initiated at Baseline visit or later in the study, if indicated by current EASL/AASLD treatment guidelines.

In particular, NA treatment should be considered if one of following conditions is met:

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

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

5.6.2. Prohibited Treatments

Treatment with the following drugs will not be permitted unless discussed with and approved by the Study Medical Monitor.

- Systemic glucocorticosteroids (inhaled glucocorticosteroids are allowed)
- Immunomodulatory agents (drugs intended for treatment of common cold are allowed)
- Antiviral drugs for HBV and/or HDV treatment, apart from study treatment and allowed nucleoside / nucleotide analogues
- Hematopoiesis -stimulating agents are allowed during interferon therapy only
- Sulfasalazine
- Ezetimibe
- Cyclosporine
- Substrates of organic anion transporting polypeptide (OATP)1B1 and OATP1B3: Atorvastatin, Bosentan, Docetaxel, Fexofenadine, Glecaprevir, Glyburide (glibenclamide), Grazoprevir, Nateglinide, Paclitaxel, Paritaprevir, Pitavastatin, Pravastatin, Repaglinide, Rosuvastatin, Simeprevir, Simvastatin (acid), Olmesartan, Telmisartan, Valsartan, Voxilaprevir [35, 36, 37, 38]
- 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 participant's condition,
- In case of abnormal laboratory results,
- In case of sample sent to central laboratory was considered to be not analysable,
- In case of necessity of dispensing of additional study materials and/ or study drug(s)

In case of early discontinuation of the study by study participant 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 participants who discontinue the study prematurely. The visit should be scheduled and performed at the earliest convenience after the decision to discontinue participant from the study. Participants prematurely withdrawn during the treatment period should complete procedures of Visit 14/ week 96.

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

6.2. Restrictions During the Study

Diet restrictions

Participants 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 participants

Women of childbearing potential must agree to use an adequate method of contraception throughout the treatment period and for 6 months after the last dose of the study medication.

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 (i.e. bilateral tubal legation 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 participant. [Periodic abstinence (e.g., 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, e.g., 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 participant 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 participants

Male participants who have female partner of childbearing potential must use an adequate method of contraception (as described above) and not to donate sperm throughout the treatment period and for 6 months after the last dose of the study medication.

The procedures to be followed if a female participant or female partner of a male participant becomes pregnant while enrolled in the study are described in Section 7.5.

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 participants 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 participant 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, benzodiazines, 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 of the eCRF.

6.3.9. Serum Alpha-fetoprotein

Serum alpha-fetoprotein will be measured for all participants at Screening. The alpha-fetoprotein test is intended to rule out hepatocellular carcinoma.

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 participants 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 participant 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 participant to visit the site, upon consent of the participants and by the decision of investigator, the blood sampling may be performed out of the site: at participant'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 participant 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.

6.4.3. HBV/HDV genotyping

HBV/HDV genotyping will be done in central virology laboratory once during the study. HDV genotyping will be done at Randomization/Baseline visit, using sequencing technique. HBV genotyping is performed at first occasion of positive result for HBV DNA in a blood sample collected for HBV DNA quantitative PCR assay starting from Baseline visit.

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.

6.4.4. NTCP Polymorphism and Resistance Tests

Blood samples for determination of NTCP polymorphism are collected at Day 1 for all the participants. NTCP polymorphism will be performed in central laboratory for participant 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 (NTCP) 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 (SNP) analysis will be performed to compare participant´s NTCP polymorphisms and the respective consensus NTCP sequence.

Blood samples for phenotypic assay are collected at Day 1 for all the participants. Baseline phenotypic assay will be performed in at least 10% of Day 1 samples, in order to determine an EC50 threshold at baseline. The five first participants from each bulevirtide treatment arm (Arms B, C and D) and three first participants from Arm A 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.

For other resistance tests (e.g. HBV genome sequencing, and HDV genome sequencing) and phenotypic assay at the other timepoints back-up virology samples are used. Resistance testing is performed in central laboratory. Details on collection, storage and transportation of samples are provided in laboratory manual.

Full resistance testing will be performed in participants for whom results of HDV RNA testing in central laboratory indicate lack of response (non-responders) or viral breakthrough using the following definitions:

Definition for Viral Breakthrough

A) Two consecutive HDV RNA values ≥ LoD (target detected) if the HDV RNA value was previously < LLoD (target not detected) at least at two consecutive time points.

   or

B) A confirmed increase of ≥ 1 $\log_{10}$ IU/mL HDV RNA from the nadir on two consecutive visits under treatment and/or until the end of treatment, assuming the nadir was previously at least 1 $\log_{10}$ IU/mL below the HDV RNA baseline value at two consecutive visits.

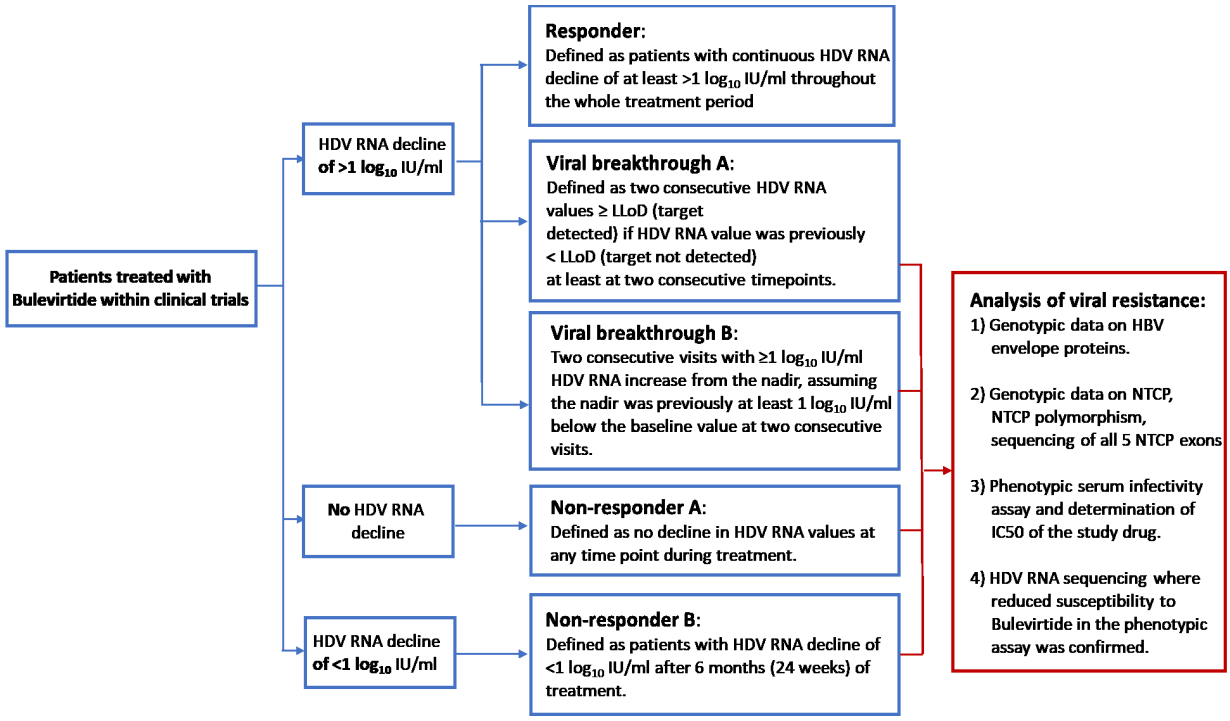
Definition for Non-Responder

A) No decline in HDV RNA values at any time point during treatment

   or

B) A less than 1 $\log_{10}$ IU/mL decline in HDV RNA after 6 months (24 weeks) of treatment.

The decision tree for selection of participants for resistance testing is provided below.



HBV genome sequencing

Partial sequencing of HBV genome will be performed with the focus on the HBV envelope open reading frame (ORF) for the L, M, S genes. Baseline isolates are compared with isolates of virological failure or timepoints were no response to the study drug was observed.

Phenotypic assay

An *in vitro* infectivity assay will be performed to determine the EC50 of bulevirtide at baseline and at the time of the virological failure. The following results will be obtained:

- EC50 value of baseline sample
- EC50 values determination of at least 10% of all BL samples in order to define resistance threshold.
- EC50 value of reference strain (lab virus stock)
- EC50 value of sample at the time of virological failure
- Fold resistance change calculation = EC50 value at the time of failure / EC50 of reference strain
- Fold resistance change calculation = EC50 value at the time of failure / EC50 of baseline

HDV genome sequencing

Whole genome sequencing for HDV genome is performed in cases where a reduced susceptibility to bulevirtide in the phenotypic assay was confirmed. Baseline isolates are compared with isolates of virological failure or timepoints were no response to the study drug was observed.

Blood samples collected within the study can be analyzed for other parameters for further investigational purposes.

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 the study site. If agreed with Medical Monitor and Project Manager, liver biopsy can be performed in other institution or any other study site.

Liver biopsy samples should be collected if feasible at Screening and week 72 (Arm A) and week 120 (Arms B, C, and D) 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 biopsy should not be performed.

Participants 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 participant eligibility, he should contact Medical Monitor prior to biopsy. If liver biopsy was performed within 1 year prior to Screening, and a participant 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 the study site. If agreed with Medical Monitor and Project Manager, Fibroscan can be performed in 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, i.e. adverse events monitoring.

6.5.1. Physical Examination

A complete physical examination is 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 CRF as medical history and its importance for including the participant into the study must be considered. Any clinically significant worsening of conditions which were present at baseline (last assessment before study drug administration) or clinically significant worsening as a result of study procedure must be reported as adverse event in the eCRF.

Complete Eye Examination

Decrease or loss of vision, retinopathy including macular edema, retinal artery or vein thrombosis, retinal hemorrhages and cotton wool spots, optic neuritis, papilledema and serous retinal detachment are induced or aggravated by treatment with alpha interferons. All participants should receive an eye examination at Screening. Participants with pre-existing ophthalmologic disorders (e.g., diabetic or hypertensive retinopathy) should receive periodic ophthalmologic exams during interferon alpha treatment. Any participant who develops ocular symptoms should receive a prompt and complete eye examination. Interferon alpha treatment should be discontinued in participants who develop new or worsening ophthalmologic disorders.

Ophthalmologic exams can be performed at any institution by any qualified specialist, i.e. it is not necessary to perform the procedure at the study site.

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 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 Participants 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 Adverse Event 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 Participants Enrolled in Preventive Vaccine Clinical Trials" and the Grade according to 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 Participants 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 participant 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 adverse event or not. See Section 7 for definition and reporting requirements for results of vital signs assessment that qualify as adverse events

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 (mmHg). 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 electrocardiogram (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 adverse events.

If, in the case of external unavoidable circumstances, including COVID-19 pandemic spread in the world, it is not possible for participant to visit the site, upon consent of the participants and if agreed with Medical Monitor and Project Manager, ECG can be performed in other institution or any other study site.

6.5.4. Hematology, Biochemistry, Coagulogram, Vitamin D and TSH

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 (e.g. 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 participants 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 adverse event or not. See Section 7 for definition and reporting requirements for results of laboratory tests that qualify as adverse events.

Hematology will include:

- Hematocrit
- Hemoglobin
- Platelets
- Reticulocytes
- Red blood cell (RBC) count
- White blood cell (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
- 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, levels of Vitamin D and TSH (only for Arms A, B, C) are 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 analyzed 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 participants 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 adverse event or not. See Section 7 for definition and reporting requirements for results of laboratory tests that qualify as adverse events.

6.5.7. Adverse Events

See Section 7.

6.6. Other Procedures

6.6.1. Immunogenicity

Bulevirtide antibodies will be determined at central laboratory for B, C and D Arms only. Schedule of blood sampling is given in Table 1. Samples for immunogenicity assessment should be taken before administration of the study drug. ELISA method will be used for analysis.

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

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. Pharmacokinetics samples are taken only for Arms B, C and D.

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 post bulevirtide injection.

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. Participant Diary

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

- Date and time of each bulevirtide and/ or Peginterferon alfa-2a dosing
- Adverse events experienced by a participant

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

6.8. The Quality of Life Questionnaires

The quality of life questionnaires will be completed by the participants as indicated in Table 1. The following questionnaires will be given to participants:

- EuroQol 5-Dimentions (EQ-5D)
- Fatigue Severity Scale (FSS)
- The Hepatitis Quality of Life Questionnaire™ (HQLQ™)

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; hepatocellular carcinoma development; liver transplantation; liver related hospitalization: amount of hospitalizations and duration of each period of 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 participant or clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (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 study drug administration (e.g. ALT elevation before study drug administration) should not be reported as adverse event unless a notable deterioration has occurred or SAE has occurred after signature of informed consent.

7.1.2. Serious Adverse Event (SAE)

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 participant 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 adverse event or a serious adverse event:

- Hospitalization for respite care,
- Planned hospitalization required by the protocol (e.g. 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 participant has not experienced an adverse event,

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse but should be reported as an adverse event instead:

- Hospitalization that was necessary because of participant 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 participant 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 Injection Sites

Local reactions at the injection sites belong to adverse event of special interest 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; hepatocellular carcinoma development; liver transplantation; liver related hospitalization: amount of hospitalizations and duration of each period of 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 adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms,
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation),
- Results in a medical intervention (e.g., 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 adverse event.

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 adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event 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 Adverse Event eCRF. If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event.

7.1.5. Abnormal Vital Sign Values

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

- Is accompanied by clinical symptoms,
- Results in a change in study treatment (e.g., dosage modification, 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 adverse event.

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 adverse event is at least a reasonable possibility, i.e., 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 (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product) (ICH E6).

Suspected Unexpected Serious Adverse Reaction (SUSAR):

Serious ADR that is classified as unexpected, i.e. 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 adverse event should follow the NCI-CTCAE (version 5.0), and the highest level of severity that the adverse event 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	Severity	Definition
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 participant.
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 participant 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 injections site.

7.2.2. Relationship to Study Medication

For all collected AEs, the investigator who examines and evaluates the participant 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 (i.e. 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 participant is stabilized, but with sequelae from this AE
Recovering/resolving:	The participant is recovering from this AE/this AE is resolving.
Fatal:	The participant 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 adverse events at each participant contact. All adverse events, whether reported by the participant or noted by study personnel, will be recorded in the participant's medical record and on the Adverse Event 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 (e.g., 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 initiation of study treatment 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 (e.g. biopsy) also should be reported.

7.3.2. Adverse Event Reporting

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event 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 drug(s) 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, and outcome, 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 (e.g. 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

PPD

NOTE: Before sending the SAE report, please inform Clinical research associate (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 Adverse Event 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.

The study sponsor will be responsible for notifying the manufacturer of Peginterferon alfa-2a of any serious adverse reaction related to Peginterferon alfa-2a.

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 serious adverse events 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 participant becomes pregnant, the investigator must:

- **Withdraw the participant 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 participant receiving/ received bulevirtide becomes pregnant, the investigator should propose signing of the Information Sheet for pregnant partner and Informed Consent Form to the provision of information about pregnancy and its outcome.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Populations

Enrolled set: All participants screened and enrolled (signed Informed Consent) into this study.

Randomized set: All enrolled and randomized participants.

Full analysis set (FAS): All participants randomized who received study medication (pegylated interferon and/or bulevirtide) at least once after randomization.

Per-protocol (PP) set: All participants of the FAS for whom no protocol deviations are judged to have an impact on the analysis of the primary efficacy endpoint of SVR 24. Details will be specified in the statistical analysis plan and final decision on exclusion from PP set will be made in a data review meeting before database lock.

Safety population: All participants who had been exposed to study mediation (pegylated interferon and/or bulevirtide)

Analyses based on the randomized set and the FAS will use the randomized treatment. Analyses based on the PP population and the Safety population will use the actual treatment received.

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 participants in the FAS and the PP population. Presentation for Safety, and Randomized set (if applicable) will be done if the corresponding set size differs from the FAS set size by more than 10%.

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 visit.

<u>Primary Analysis</u>

The primary efficacy analysis of this study is the estimation of the difference in rates between the combination of pegylated interferon + bulevirtide 10 mg (Arm C) and bulevirtide 10 mg monotherapy (Arm D) of sustained virological response (SVR 24) defined as undetectable HDV RNA at FU-24 after the scheduled end of treatment. A 95%-confidence interval with exact

unconditional confidence limits using the score statistic will be presented for the rate differences. Clopper-Pearson 95%-confidence intervals will be calculated for the single rates. The p-value of a two-sided Fisher test will be calculated.

Participants with missing FU-24 assessment in HDV RNA will be handled as non-responders unless it is related to COVID-19 in which case missing values will be imputed using the next observation carried backward (NOCB) approach.

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.

The influence of covariables e.g. presence of cirrhosis and region will be investigated using logistic models.

CCI [redacted]

8.2.3. Analysis of Safety

Adverse Events

Adverse events (AE) will be coded using MedDRA and will be presented by primary SOC and Preferred Term (PT). The analysis will focus on the treatment-emergent AEs (TEAE), i.e., AEs which started or worsened after start of treatment and no later than 30 days after permanent discontinuation of treatment. The frequency of TEAEs will be summarized by incidences. In these summaries, each participant will be counted only once within each preferred term 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 dose reduction and AE 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).

ECG

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

Immunogenicity

The production of bulevirtide antibodies will be presented by visit.

Pharmacokinetics

Plasma concentration of bulevirtide will be described by descriptive statistics.

Other Safety Assessments

Other safety variable will be described by appropriate descriptive statistics.

8.2.4. Determination of Sample Size

The primary efficacy analysis of this study is the estimation of the difference in rates between the combination of pegylated interferon + bulevirtide 10 mg (Arm C) and bulevirtide 10 mg

monotherapy (Arm D) of sustained virological response (SVR 24) defined as undetectable HDV RNA at week 24 after the scheduled end of treatment i.e. at study week 120. With 48 participants per treatment group a two-sided continuity corrected 95%-confidence interval for the difference of the SVR 24 rates will extend less than 22.5% from the observed difference. The sample size will be slightly increased to 50 participants per treatment group to account for a few potential early withdrawals before exposure.

The treatment group with the combination of pegylated interferon + bulevirtide 2 mg will be of the same size. The treatment group with the pegylated interferon will include 25 participants. Hence 175 participants will be randomized.

8.2.5. Interim, Follow-up and Final Analyses

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

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2) When all participants complete the FU-24 visit or discontinue the study (FU-24 main primary analysis).

3) When all participants complete the final follow-up visit at 48 weeks after the scheduled end of treatment (FU-48) or discontinue the study (FU-48 final analysis: analysis of all collected data from the study).

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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.

If, in the case of external unavoidable circumstances, including COVID-19 pandemic spread in the world, On-site visit is impossible, remote monitoring will be performed, given that all regulatory and essential data protection requirements are met and appropriate arrangements to ensure participants' 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 (IEC) and/or Institutional Review Board (IRB)

The protocol, informed consent form(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 consent form 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 consent form 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.

If, in the case of external unavoidable circumstances, including COVID-19 pandemic spread in the world, it is not possible for participant to visit the site, however, any urgent measures need to be implemented in the interest of participant's safety, informed consent can be received receive the participant's oral consent by phone supplemented with an email confirmation (if it is

possible) before the respective action. Updated participant information sheet and consent form 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 participants participating in the study. Therefore, the eCRFs should be completed as soon as possible during or after the participant'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 participants 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.

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APPENDIX 1. CONFIRMATION OF PARTICIPANTS' 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 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 transaminase level >1 × ULN, but less than 10 × ULN	Central Lab test report
6	Serum albumin >28 g/L	Central Lab test report
7	Thyroid stimulating hormone (TSH) within normal ranges (including on medication for control of thyroid function)	Central Lab test report
8	Negative urine pregnancy test for females of childbearing potential	Urine pregnancy test result at site documented in medical records
9	Female participant: Postmenopausal for at least 2 years	Assessed and documented by Investigator in medical record
	Female participant: Surgically sterile (total hysterectomy or bilateral oophorectomy, bilateral tubal ligation, staples, or another type of sterilization)	
	Female participant: Abstinence from heterosexual intercourse throughout the treatment period	
	Female participant: Willingness to use highly effective contraception (double barrier method or barrier contraception in combination with hormonal or intrauterine contraceptive) throughout the treatment period and for 6 months after the last dose of the study medication	
10	Male participants 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 treatment period and for 6 months after the last dose of the study medication	Assessed and documented by Investigator in medical record

Exclusion Criteria		Confirmation
1	Child-Pugh hepatic insufficiency score of B-C or over 6 points. NOTE: Child-Pugh hepatic insufficiency score of 6 points is allowed. Only participants with compensated cirrhosis are allowed. Uncomplicated oesophageal varices allowed; Participants 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 HIV co-infection. Participants with HCV antibodies can be enrolled, if screening HCV RNA test is negative	Central Lab test report
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. [Participants 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	NYHA (New York Heart Association) class III-IV congestive heart failure	Assessed and documented by Investigator in medical record
8	Participants 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 participant's enrolment into the study	Assessed and documented by Investigator in medical record

Exclusion Criteria		Confirmation
10	Participants 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 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 (e.g., 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 participants 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 participants)	Central Lab test report
14	Absolute neutrophil count < 1500 cells/mm^3 (<1000 if African participants)	Central Lab test report
15	Platelet count < 90,000 cells/mm^3	Central Lab test report
16	Hemoglobin < 12 g/ dL	Central Lab test report
17	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
19	History of solid organ transplantation	Assessed and documented by Investigator in medical record
20	Current alcohol abuse or alcohol abuse within 6 months prior to enrolment in this study; current drug addict or history of drug use within 2 years prior to Screening	Alco-test result at site documented in medical record; Assessed and documented by Investigator in medical record

Exclusion Criteria		Confirmation
21	History of disease requiring regular use of systemic glucocorticosteroids (inhalative glucocorticosteroids are allowed) or other immunosuppressants	Assessed and documented by Investigator in medical record
22	Pregnant or breast-feeding females	Pregnancy urine test result at site documented in medical record; Assessed and documented by Investigator in medical record
23	Participation in another clinical study with investigational study drug within 30 days prior to randomization	Assessed and documented by Investigator in medical record
24	Receipt of bulevirtide previously, e.g. in clinical trials	Assessed and documented by Investigator in medical record
25	Inability to follow protocol requirements and undergo all protocol procedures. NOTE: Participants with medical contraindication for liver biopsy are allowed to participate in this study. Such participants will exempt from liver biopsy requirements in this study. Participants 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
26	Contraindications, intolerance or hypersensitivity to interferons alfa, genetically engineered E.coli medications, polyethylene glycol or other components of peginterferon alfa.	Assessed and documented by Investigator in medical record
27	Presence or history of severe retinopathy, significant diabetic or hypertensive retinopathy.	Copy of ophthalmologic examination's results performed during Screening period Assessed and documented by Investigator in medical record
28	Uncontrolled diabetes mellitus.	Assessed and documented by Investigator in medical record
29	Uncontrolled cardiovascular disorders within 6 months before screening.	Assessed and documented by Investigator in medical record
30	History of autoimmune disorder (e.g. myositis, hepatitis, thrombotic thrombocytopenic purpura, idiopathic thrombocytopenic purpura, severe psoriasis, rheumatoid arthritis, interstitial nephritis, thyroiditis, and systemic lupus erythematosus)	Assessed and documented by Investigator in medical record

Exclusion Criteria		Confirmation
31	Presence or history of significant psychiatric disorder (e.g. severe depression, suicide attempt, severe neurosis or cognitive disorder).	Assessed and documented by Investigator in medical record
32	Presence or history of chronic lung disease with respiratory malfunction.	Assessed and documented by Investigator in medical record

protocol MYR204 Amendment 4

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
CCI	Clinical Research eSigned	PPD