Statistical Analysis Plan

Study Information:

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Document History

Version	Modified by (name and role)	Date	Description of Changes
1.0	PPD Senior Biostatistician	2020-09-28	Final version
2.0	PPD Senior Biostatistician	2020-09-30	AEs by ADA pos./ADA neg. added. Calculation of number of missed doses adjusted Final version
2.0 incorporating SAP Amendment	PPD Senior Biostatistician	2021-03-19	For description of changes see SAP Amendment
3.0	PPD Senior Biostatistician	2021-08-20	NTCP polymorphism and resistance removed from analysis. MMRM replaced with ANCOVA for serum alpha-2-macroglobulin at Week 48 analysis. Tables for prior and concomitant HBV medications added.
4.0	PPD Sr Director, Biostatistics, Gilead PPD Senior Biostatistician	2022-10-25	Remove per protocol (PP) analysis for W96 and W144 analyses, revise PP analysis set definition for W168 analysis, reduce scope of PP analysis; Revise TEAE definition, add imputation method for incomplete AE start/stop date; Add exploratory endpoint "HDV RNA decrease by ≥2 $\log_{10}$ IU/ml from baseline or undetectable HND RNA at all postbaseline assessments"; Correct imputation on safety laboratory data below LLOQ or above ULOQ; Correct Knodell fibrosis score stages system to be consistent with database; Updated description of the identification of missing doses and the computation of total dose administered; Categorisation of HAI scores; Revise potential liver related events.

Table of Content

1 Acronyms and Abbreviations used in the Document

Abbreviation	*Explanation*
ADA	Anti-drug antibodies
AE	Adverse Event
AFP	Serum alpha fetoprotein
ALT	Alanine transferase
AST	Aspartate transferase
ATC	Anatomical Therapeutic Chemical [classification system]
BMI	Body mass index
CHD	Chronic hepatitis delta
COVID-19	Coronavirus disease 2019
CI	Confidence interval
CRF	Case report form
CRP	C-reactive protein
CS	Clinically Significant
CTCAE	Common Terminology Criteria for Adverse Events
DDP	Data display plan
DNA	Deoxyribonucleic acid
DRM	Data Review Meeting
ECG	Electrocardiogram
eCRF	Electronic case report form
EOS	End of study
EQ-5D	EuroQol 5-Dimentions
FAS	Full analysis set
FSS	Fatigue Severity Scale
GGT	Gamma glutamyl transferase
HBeAg	Hepatitis B virus e-antigen
HBsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B virus
HIV	Human immunodeficiency virus
HDV	Hepatitis delta (D) virus
HQLQ™	Hepatitis Quality of Life Questionnaire™
IAP	Interim Analysis Plan
IC50	half maximal inhibitory concentration
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IMP	Investigational medicinal product

Abbreviation	*Explanation*
INR	International normalised ratio
kPa	Kilopascal
LOD	Limit of detection
LLoQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MEF	Missing Equals Failure
MMRM	Mixed-effects model for repeated measures
NCS	Not Clinically Significant
NTCP	Sodium taurocholate co-transporting polypeptide
PCR	Polymerase chain reaction
PK	Pharmacokinetic
PP	Per-protocol
RBC	Red blood cell count
REML	Restricted maximum likelihood
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SVR24	Undetectable HDV RNA 24 weeks after scheduled end of treatment
SVR48	Undetectable HDV RNA 48 weeks after scheduled end of treatment
ULOQ	Upper limit of quantification
VAS	Visual Analogue Scale
WBC	White blood cell count
WT	wild type

2 Introduction

The Statistical Analysis Plan (SAP) is a complementary document to the Clinical Study Protocol and includes a more technical and detailed elaboration of the principal features of the proposed statistical analysis and presentations, and the way in which anticipated analysis problems will be handled.

If the SAP suggests changes to the principal features stated in the protocol, these should also be documented in a protocol amendment. Otherwise, it will suffice to record the changes in the SAP.

A separate virology analysis plan will be prepared by the sponsor to provide details of the analysis of NTCP polymorphism and resistance testing (phenotyping assay and genome sequencing) data.

This SAP version (version 4.0) will be applied to the analysis conducted at W96, W144, W168 and W240 (final analysis). For analyses conducted at W24 and W48, please refer to the SAP version 2.0 and version 3.0 respectively.

3 Study Objectives

3.1 Primary Objective

To evaluate the efficacy of bulevirtide administered subcutaneously for 48 weeks at a dose of 2 mg or 10 mg once daily for treatment of chronic hepatitis delta in comparison to delayed treatment.

3.1.1 Primary Variables

The primary variable is the combined response at week 48.
Combined response is defined as fulfilment of two conditions simultaneously:

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

3.2 Secondary Objectives

The secondary objectives are:

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

The exploratory objectives are:

- To investigate the immunogenicity of bulevirtide;
- To investigate influence of bulevirtide on quality of life;
- HBV/HDV genotyping;
- Resistance testing.

3.2.1 Secondary Efficacy Variables

The secondary efficacy variables are:

- Undetectable HDV RNA at week 48;
- ALT normalization at week 48;
- Undetectable HDV RNA 24 weeks after scheduled end of treatment (sustained virological response, SVR24);
- Undetectable HDV RNA 48 weeks after scheduled end of treatment (sustained virological response, SVR48);

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- Adverse events (treatment emergent);
- 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 (haematology, coagulogram, biochemistry, blood bile salts, vitamin D).

3.2.5 Pharmacokinetic variables

Plasma concentration of bulevirtide.
Sampling is done 1 hour ± 15 min post bulevirtide injection. During first 48 weeks pharmacokinetics samples will be collected only for Arms B and C (not from the delayed treatment group).

3.2.6 Other Variables

- HDV/HBV genotyping;
- NTCP polymorphism (only in non-responders and patients with virological breakthrough);
- 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 patients with positive HBeAg at SCR)
- Other parameters in liver biopsy samples.

4 Study Design

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

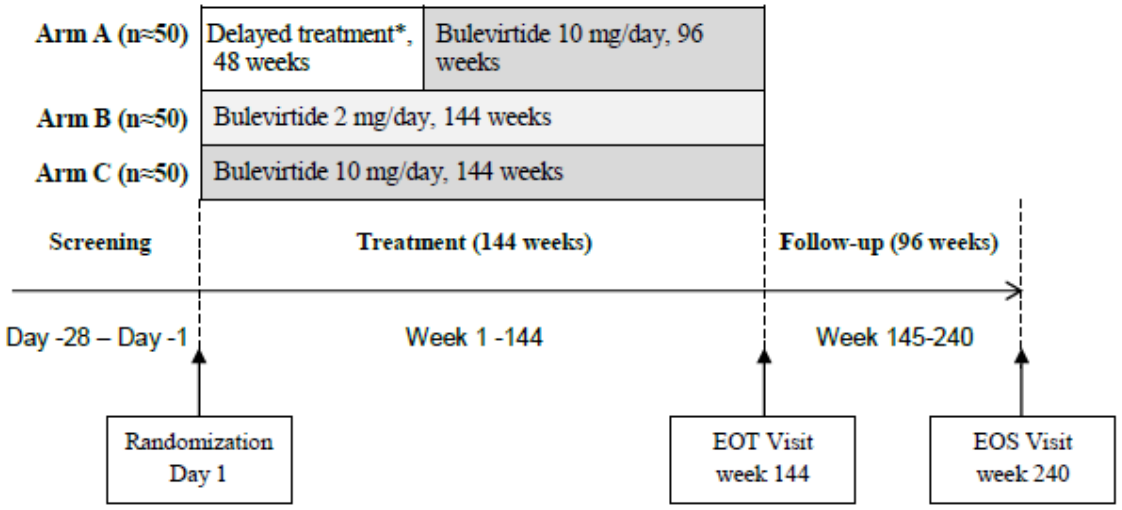
This study will be conducted at approximately 24 sites across approximately 5 countries globally which may include Germany, Russia, Italy, Georgia and USA. A total of 150 subjects will be randomized.

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

At week 48, CHD patients from the delayed treatment group (arm A) will be switched to bulevirtide 10 mg/day for 96 weeks.

The total duration of treatment period is 144 weeks. After completion of the treatment period, subjects will be followed for additional 96 weeks. For all subjects the total amount of time to complete the study will be 240-244 weeks (inclusive of the Screening, Treatment, and Follow-Up Periods).

A scheme of the study design is presented in Figure 1. The schedule of events to be conducted during the 144-week Treatment Period and the safety Follow-Up Period is presented in Table 1. Treatment and all study procedures will be performed on an outpatient basis.



EOT: End of treatment; EOS: End of study

*Delayed treatment means no treatment for HDV infection for 48 weeks.

5 Study Population

This study plans to randomize a total of 150 adult male and female patients (18-65 years) with chronic HDV infection and elevated ALT at Screening.

5.1 Sample Size

To account for the repeated analysis of response (interim at 24 weeks and main analysis at 48 weeks) the nominal two-sided significance level of 0.05 will be split among the time points with 0.01 for 24 weeks leaving 0.04 for 48 weeks. At each time point the bulevirtide doses will be compared to delayed treatment in terms of a hierarchical testing procedure starting with the higher dose at the respective adjusted two-sided significance levels.

The expected response rates at 48 weeks for the bulevirtide 2mg and 10mg doses are 45% or greater. The conservative expectation for the delayed treatment response rates is 8% or less. These assumptions are based on results from preceding phase 2 study (MYR 202).

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

This sample size will be slightly increased to 50 patients per treatment group to account for a few potential early withdrawals before exposure. Hence 150 patients will be randomized.

6 Assessments

A schedule of assessments from the protocol is presented in Appendix 1.

6.1 Impact of COVID-19 on Assessments and Study Procedures

Due to the ongoing coronavirus disease 2019 (COVID-19) pandemic, extraordinary measures may need to be implemented and trial management may need to be adjusted due to unavoidable circumstances, *e.g.* self-isolation/quarantine of trial participants, limited access to public places (including hospitals) and/or public transportation as well as health care professionals being committed to critical tasks.

This can have an impact on the study procedures and subjects' attendance of scheduled study visits.

If it is not possible for subjects to visit the sites, blood and urine sampling for efficacy and safety analysis, and ECG assessments may be performed out of the site, and study medication may be delivered to the subject.

All protocol deviations related to COVID-19 will be classified as "COVID-19 related".

6.2 Efficacy assessments

6.2.1 Virology

Blood samples for virology tests will be collected according to the schedule of assessments and analysed by the central virology laboratory. The following virology tests will be performed

- HDV RNA by a quantitative PCR;
- HBV DNA by a quantitative PCR;
- HBsAg level by a quantitative immunoassay;
- HBeAg and HBeAg antibodies (only if patient is HBeAg positive at Screening);
- HBsAg antibodies.

Virology test	Lab name	LLOQ	LOD
HDV RNA	Frankfurt provided by MLM	50 IU/mL	6 IU/mL
HBV DNA	Frankfurt provided by MLM	10 IU/mL	10 IU/mL
HBsAg	Frankfurt provided by MLM	N/A	0.05 IU/mL

For the screening HBV DNA values (e.g. from Invitro[1])which displays character result as "< 10^2", the numeric value will be imputed as 50 for statistical analysis; for the screening HBV DNA values which displays character result as "Is not detected" with comments of "Sensitivity detection 20 IU/ml", the numeric value will be imputed as 10 for statistical analysis.

[1] The HBV DNA data provided by Invitro is categorised as a serology parameter in the data transfer specification.

6.2.2 ALT

The ALT test results from the safety blood samples for clinical chemistry testing will be used for efficacy analyses.

6.2.3 Transient Elastometry

Transient elastography to assess hepatic fibrosis staging will be performed using FibroScan at Screening, Week 48, 96, 144, 192 and 240.

6.2.4 Liver Biopsy

Liver biopsy samples will be collected at Screening and Week 48. If there are available appropriate biopsy specimens from within 1 year prior to Screening, these can be used for the baseline evaluation, and biopsy at Screening is not required.

The histological activity index (HAI) is an additive score calculated as the sum (range 0–18) of the semi-quantitative scores for 3 individual features: periportal and/or bridging necrosis, hepatocyte degeneration and/or focal necrosis, and portal inflammation.

The Knodell fibrosis score stages fibrosis in a 5-tier system:

0. Fibrosis is absent
1. Fibrous expansion of portal tracts
2. Expansion of portal tracts + portaportal septa
3. Bridging fibrosis – portaportal or portocentral septa
4. Cirrhosis.

The Ishak fibrosis score is part of the Ishak score, a modified form of the HAI, and has 7 stages:

0. No fibrosis
1. Fibrous expansion of some portal areas, with or without short fibrous septa
2. Fibrous expansion of most portal areas, with or without short fibrous septa
3. Fibrous expansion of most portal areas with occasional portal to portal bridging
4. Fibrous expansion of portal areas with marked bridging (portal to portal as well as portal to central)
5. Marked bridging (portal–portal and/or portal–central) with occasional nodules (incomplete cirrhosis)
6. Cirrhosis, probable or definite

The METAVIR scoring system is used to assess the extent of inflammation and fibrosis by histopathological evaluation in a liver biopsy. It comprises two scores, the fibrosis stage representing the amount of fibrosis or scarring, and the activity grade indicating the degree of inflammation:

- Fibrosis stage:
  F0: No fibrosis
  F1: Portal fibrosis without septa
  F2: Portal fibrosis with few septa
  F3: Numerous septa without cirrhosis
  F4: Cirrhosis
- Activity grade:
  A0: No activity
  A1: Mild activity
  A2: Moderate activity
  A3: Severe activity

The analysis of the liver biopsy samples also includes molecular analysis of HDV RNA, HBV RNA and DNA, and HDAg, and analysis of gene expression of CXCL10, NTCP, CYP7A1, ISG15, MX1, OAS, HLA-E, TAP1, and USP18.

6.2.5 Serum Alpha-2-macroglobulin

Blood samples for testing for the serum fibrosis marker, alpha-2-macroglobulin, will be collected at Day 1, Weeks 48, 96,144,168 and the last follow-up visit and analysed by central laboratory.

6.3.1 Adverse Events

The reporting period for serious adverse events starts after informed consent has been obtained and ends at the end of study visit.

The reporting period for non-serious adverse events starts with the initiation of study treatment and ends at the end of study visit. Non-serious events occurring during the screening period which are judged to be related to study procedures should also be reported.

The severity of adverse events will be assessed according to the NCI-CTCAE (version 5.0), and the highest observed severity grade for each event will be reported. Events for which a CTCAE term cannot be found will be assigned a severity grade according to the definitions in section 7.2.1. of the clinical study protocol. For each event, the highest severity grade observed will be reported.

Local reactions at the injection sites and the following liver related clinical events are considered as adverse events of special interest:

- Cirrhosis development.
- Development or worsening of jaundice.
- Development or worsening of coagulopathy.
- Development or worsening of ascites.
- Development or worsening of hepatic encephalopathy.
- Bleeding from oesophageal varices.
- Hepatocellular carcinoma development.
- Liver transplantation.
- Liver related hospitalisation: number of hospitalisations and duration of each period of hospitalisation.
- Liver related death.

A list of dictionary terms used to identify these liver related clinical events is given in Appendix 2.

6.3.2 Physical Examination

A complete physical examination will be performed at Screening, Randomisation (Visit 1), and Weeks 24, 48, 96 and 144 including assessments of the following body systems:

- general appearance;
- skin;
- head, eyes, ears, nose and throat;
- lymph nodes;
- respiratory;
- cardiovascular;
- gastrointestinal,
- musculoskeletal;
- endocrine;
- nervous systems;
- urogenital

At all other visits, a symptom directed physical examination is performed.

At each visit during the treatment phase, and at the first follow-up visit, an assessment of local reactions at the injection sites will be made, and the severity grade of four pre-specified types of reactions (pain; tenderness; erythema/redness; induration/swelling) will be reported. The severity grade will be reported according to the criteria for clinical abnormalities defined in Table A of the FDA Guidance for Industry 'Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials'.

6.3.3 Vital Signs

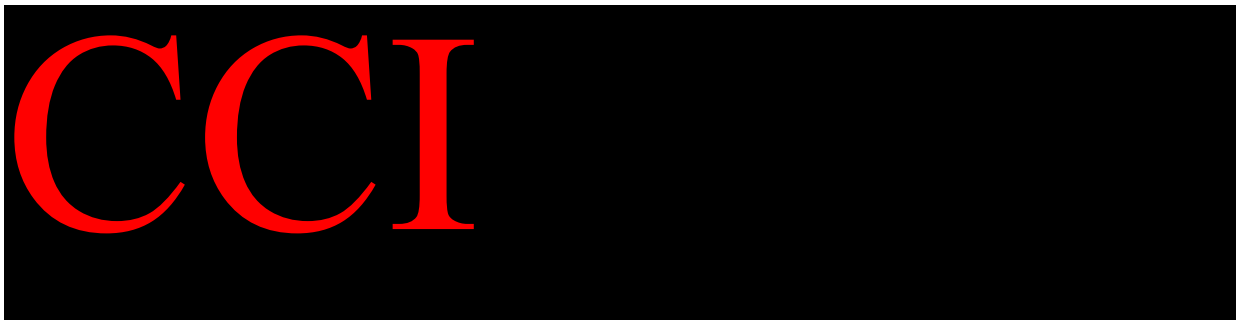
Measurements of blood pressure, heart rate, respiratory rate and body temperature will be performed at all visits.

6.3.4 Electrocardiogram

A 12-lead electrocardiogram (ECG) will be recorded at Screening, and at Weeks 8, 24, 48, 72, 96, 120, and 144,192 and 240. Assessments of heart rate, QRS, RR, PQ, QT and QTc intervals, using Bazett's formula for the correction for heart rate, will be made, as well as a general assessment of whether the ECG results were normal or abnormal and the clinical significance of abnormal results.

6.3.5 Safety Laboratory Assessments

Samples for haematology, biochemistry, coagulogram, vitamin D, total blood bile salts and urinalysis will be analysed by the central laboratory.



accumulation in plasma. Analysis will be done by central laboratory.
Blood sample for estimation of drug concentration will be collected at Randomization/Baseline visit and all Treatment visits after the start of bulevirtide therapy. Sampling should be done 1 hour ± 15 min post bulevirtide injection. During first 48 weeks pharmacokinetics samples will be collected only for arms B and C. After week 48, pharmacokinetic samples are taken for all three arms.

6.6 Other Assessments

6.6.2 NTCP Polymorphism and Resistance Tests

Samples for determination of NTCP polymorphism will be collected at Day 1. Polymorphism will be performed by central laboratory for subjects for whom results of HDV RNA indicate lack of response or viral breakthrough.

Blood samples for phenotypic assay will be collected at Day 1 for all the patients. Baseline phenotypic assay will be performed for at least 10% of the Day 1 samples, in order to determine an EC50 (half maximal effective concentration) threshold at baseline. The five first patients from each arm after randomisation will be included into the analysis, based on their baseline HDV RNA titer which is supposed to be at least 1 000 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.

Full resistance testing will be performed in patients for whom results of HDV RNA testing in central laboratory indicate lack of response or viral breakthrough.

For more details on the assessments of NTCP polymorphism and resistance tests, see section 6.4.4 of the clinical study protocol.

6.6.3 Demographics and Anthropometrics

Demographic data (date of birth, sex and race) will be collected at Screening.

Body weight will be measured at every visit, and height will be measured at Screening.

6.6.4 Substance Use

An assessment of substance use (smoking/alcohol/drugs) will be done at screening. Information about the status (non-user, former user, current user) and the frequency of use will be collected.

In addition, the alcohol levels in exhaled oxygen will be measured at Screening and Randomisation, and a urine drug test (amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, methadone, opiates, and tricyclic antidepressants) will be performed at Screening.

6.6.5 Abdominal Ultrasound

Abdominal ultrasound will be done at Screening.

6.6.6 Urine Pregnancy Test

Required for women of childbearing potential. Pregnancy test will be performed at Screening and during the study.

6.6.7 Serum Alpha-fetoprotein

Serum alpha-fetoprotein will be measured for all subjects at Screening.

6.6.8 Serology Tests

Samples for serology tests will be collected at Screening and analysed by central laboratory. The following tests will be performed:

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

In case of positive test result for HCV antibodies, a qualitative test of HCV RNA must be done; the subject can be enrolled into the study if the latter is negative

6.6.9 Medical History

The following information will be collected:

- Information about diseases, conditions and surgeries related to the liver (collected for a lifelong period);
- Information about other diseases, conditions and surgeries (collected if occurred within 5 years before screening or regardless of the time if they are considered to be relevant by Investigator).

6.6.10 Prior and Concomitant Medications

The following information will be collected:

- All previous treatment for viral hepatitis;
- Prior therapy for other diseases for therapies that patient receives currently and therapies that were discontinued within 3 months before Screening;
- Concomitant medication.

7 Method of Analysis

7.1 General

All statistical analyses will be performed in accordance with the ICH E9 guideline for Statistical Principles for Clinical Trials (1), using SAS® (Version 9.4 or higher, SAS Institute Inc., Cary, NC, USA).

7.1.1 Presentation of Results

All results will be presented by treatment group and in total, unless stated otherwise.

It will be clearly stated which unit applies to each presented variable.

Continuous data will be summarised using descriptive statistics, and the following parameters will be reported:

- number of subjects with evaluable observations and missing observations
- arithmetic mean and standard deviation
- median and IQR

- first and third quartiles
- minimum and maximum.

Categorical data will be presented using absolute frequency and percentage. When the absolute frequency is zero, the percentage will not be presented. Unless stated otherwise, the denominator for percentage calculations will be the total number of subjects in the applicable analysis set, including subjects with missing data.

For variables with missing values, the number and percentage of subjects with missing values will be presented.

Significance tests will be two-sided and performed at the 5% significance level, unless stated otherwise. When reporting the results of significance tests, p-values will be presented.

All confidence intervals will be two-sided with a nominal confidence of 95% for within groups and if not stated otherwise.

Data will be presented using an appropriate number of decimal places, to ensure that undue precision is not implied (e.g. the number of decimals should not exceed the accuracy of the measuring instrument). Raw data will be presented with the same number of decimals as collected, and derived data with an appropriate number of decimals based on general practice, mathematical rationale or scientific rationale.

Minimum and maximum values will be presented with the same number of decimals as the analysed variable and the other descriptive statistics will be presented with one decimal more. Percentages and proportions will be presented with one decimal. Odds ratios and hazard ratios will be presented with 3 decimals, and small and large values will be presented as '<0.001' and '>999.999' respectively. Confidence interval bounds will be presented with the same number of decimals as the corresponding point estimate, and p-values will be presented with 4 decimals or as '<.0001'.

Mock tables and graphs are presented in the Data Display Plan (DDP), which is a supplementary document to this analysis plan. Individual subject data listings will be presented according to the ICH E3 guideline for Structure and Content of Clinical Study Reports (2), unless stated otherwise.

7.1.2 Baseline

The baseline value for a parameter is defined as the last non-missing value before the first dose of the investigational medicinal product (IMP) for bulevirtide 2 and 10 mg and last value before or at randomization for the delayed treatment. For subjects randomized to the delayed treatment, after switching to bulevirtide at week 48, baseline stays as the last value before or at randomization, unless specified otherwise.

7.1.3 Analysis Relative Day

The analysis relative day for an assessment/value is defined as the time in days from the date of randomization to the date of the assessment. The date of randomization is considered as day 1, and earlier dates will correspond to a negative day.

7.1.4 Analysis Visit

An analysis visit is defined as a categorical variable used to classify values within an analysis variable into temporal or conceptual groups used for analyses.

In this study, the analysis visits will correspond to the regular study visits and will be named as 'Week X' for all post-baseline visits. However, for sustained response the analysis visits during the follow-up phase will be named 'Y weeks post-treatment'.

A separate analysis visit named 'Baseline' will be added for the baseline values.

Data reported at an 'Early discontinuation' visit in the eCRF at the same date as or within the specified visit window of a regular study visit will be associated with the analysis visit corresponding to that regular study visit.

For the analysis of primary and secondary efficacy variables, time windows will be defined for some visits, for selection of data for specific analyses. Further details on this are provided in section 7.8.

7.1.4.1 Unscheduled visits

Unless stated otherwise, data from unscheduled visits will be presented in data listings only and not included in analysis or summary tables.

Data reported at unscheduled visits during the screening period should be considered when identifying baseline values for parameters.

If a retest has been performed at an unscheduled visit because a value could not be obtained at the original visit (i.e., the value is missing at the original visit), the retest value should be mapped to the corresponding analysis visit if the date of assessment is within 30 days from the planned timepoint for the original visit and occurs before the next scheduled visit.

7.1.5 Handling of Missing Data

In general, imputations of missing data will be made only for analyses of efficacy variable on the FAS (unless stated otherwise).

Details on the handling of missing data for efficacy variables are provided in sections 7.8.1 (primary), 7.8.2**Error! Reference source not found.** (secondary)CCI [redacted]

In analyses using a mixed-effects model for repeated measures (MMRM), missing values are handled by means of built-in maximum-likelihood based methods in the SAS® procedure used for the analysis, under the 'missing at random' assumption.

Details on the handling of values outside of limits of detection and quantification for efficacy variables and other non-safety laboratory test results are provided in section 7.1.5.1.1 **Error! Reference source not found.**.

Details on the handling of values outside limits of quantification for safety laboratory tests are presented in section 7.1.5.1.2 below.
Details on the handling of missing values for Quality of Life data are provided in section 7.1.5.2 **Error! Reference source not found.**.

Data listings will include the observed values. For derived variables, values based on imputed data might be presented in listings

7.1.5.1 Imputation of values of lab tests

7.1.5.1.1 Imputation of values based on limits of detection and quantification

The imputation described in this section will not be applicable to safety laboratory tests (i.e, biochemistry, haematology, coagulogram, urinalysis, other which includes bile salts and vitamin D). The imputation described in this section will be applied to virology lab tests, immunogenicity analysis, Pharmacokinetics (PK), molecular analysis or gene expression analysis, unless explicitly specified otherwise in the SAP.

The following rules will be applied (for the PP set as well):

- Values below the limit of detection (LOD) will be imputed as zero.
- Values below the lower limit of quantification (LLOQ) will be imputed as half the LLOQ value, unless the LLOQ is the same as the LOD, in which case the LOD rule takes precedence.
- Values above the upper limit of quantification (ULOQ), will be imputed as the ULOQ value.
- 'Non-measurable' data will be considered as missing data.

For log-10 transformed data, the following rules will be applied:

- Missing values due to untransformed values of zero will be imputed as zero if LOD > 1.
- Missing values due to untransformed values of zero will be imputed as $\log_{10}(LOD/2)$ if LOD <1.

7.1.5.1.2 Imputation of values from safety laboratory tests

The imputation described in this section will be applicable to safety laboratory tests (i.e, biochemistry, haematology, coagulogram, urinalysis, other which includes bile salts and vitamin D).

Safety laboratory data that are continuous in nature but less than the LLOQ or above the ULOQ will be reported in the form of “< xx.xx” or “> xx.xx” and will be imputed as one half of xx.xx for calculation of

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1. When all patients completed visit at Week 24 or had discontinued the study (week 24 interim analysis);
2. When all patients completed visit at Week 48 or had discontinued the study (week 48 main primary endpoint analysis);
3. When all patients completed visit at Week 96 or had discontinued the study (exploratory week 96 interim analysis);
4. When all patients completed visit at Week 144 or had discontinued the study (week 144 (end-of treatment) interim analysis).
5. When all patients completed visit at Week 168 or had discontinued the study (exploratory week 168 (FU-24) interim analysis).
6. When all patients completed visit at week 240 or had discontinued the study (week 240 final analysis: analysis of all collected data of the study).

Since this is an open label study, no separate interim analysis plans will be written. Thus, this SAP applies to all planned analyses above. The planned analyses will be performed on the current state of the data at the specific cut-off time for each of the planned analyses. However, due to protocol amendments, SAP version 2 dated September 30, 2020 was applied to Week 24 interim analysis, SAP version 3 dated August 24, 2021 was applied to Week 48 primary analysis. And SAP version 4 dated 2022-10-25 will be applied to Week 96, Week 144 interim analyses, Week 168 interim analysis and Week 240 final analysis.

The planned analyses 1-5 above will be based on available data up to the date of the last assessment associated with the visit at Week 24/48/96/144/168 (or the date of withdrawal for subjects who withdrew before that visit).

However, for study medication diary records, concomitant medications and Adverse Events, records/events with date up to but not including the date of the visit for the planned analysis will be included.

7.1.7 Multiplicity

An interim analysis will be performed on the primary endpoint at Week 24. To account for the repeated analysis and maintain the nominal two-sided significance level of 0.05 this level will be split among the interim (Week 24) and main analysis (Week 48), with allocating 0.01 to interim and 0.04 to main analysis.

Multiple group comparisons for the primary endpoint and the inclusion of a main secondary endpoint will be handled with a hierarchical testing procedure. Details are described in Section 7.8.1 and 7.8.2.

All other analyses will be considered explorative and no adjustment for multiple testing will be performed.

7.1.8 Subgroups

The following subgroups will be defined:

- Based on presence of cirrhosis (stratification factor):
  - Subjects with cirrhosis;
  - Subjects without cirrhosis.
- Based on anti-drug-antibodies (ADA):

- ADA positive subjects;
- ADA negative subjects.

The following two regions will be defined:

- Russia
- Germany/Italy/Sweden

The definition of regions is preliminary and will be reviewed during the clean file meeting; any changes to the above definitions will be documented in the clean file report.

7.1.9 Impact of COVID-19 on Statistical Analysis

All subjects completing the study will have been in the study during the COVID-19 pandemic and might have data affected by the pandemic.

The potential impact of the pandemic is taken into account in the analysis of the primary and the key secondary efficacy variables as described in section 7.8.1. No such analyses are planned for the other secondary [redacted] efficacy variables.

At the time of each interim analysis and the main analysis, the current status of the COVID-19 pandemic should be taken into consideration, and relevant additional sensitivity analyses may be defined.

7.2 Analysis Sets

The decision on the classification of subjects to each analysis set will be taken at the data review meeting (DRM) and documented in the DRM report together with the reasons for excluding subjects from analysis sets.

7.2.1 Randomised set

The randomised set is defined as all enrolled and randomised patients. Any analyses of the randomised set will be based on the planned treatment (*i.e.* subjects will be analysed 'as randomised').

7.2.2 Full analysis set

The full analysis set (FAS) is defined as all patients either randomised to delayed treatment arm or randomized to bulevirtide and received bulevirtide at least once after randomization.

Analysis of the full analysis set will be based on the planned treatment (*i.e.* subjects will be analysed 'as randomised').

7.2.3 Per-protocol set

There will be three PP sets in the study:

- The PP 24W set (defined for the Week 24 interim analysis)
- The PP set (defined for the Week 48 primary efficacy analysis)
- The PP 168W set (defined for the Week168 interim analysis)

The PP 24W set is defined as all subjects of the full analysis set for whom no protocol deviation judged as having an impact on the interim analysis at Week 24 on the primary efficacy endpoint of combined response was reported or identified. The decision as to which protocol deviations should be considered as reason for exclusion from the PP 24W set should be made at the Week 24 DRM and documented in the DRM report.

The per-protocol set (PP) is defined as all subjects of the full analysis set for whom no protocol deviation judged as having an impact on the primary analysis at Week 48 on the primary efficacy endpoint of combined response was reported or identified.
The decision as to which protocol deviations should be considered as reason for exclusion from the PP set should be made at the Week 48 DRM and documented in the DRM report.

The PP 168W set is defined as all subjects of the full analysis set for whom no protocol deviation judged as having an impact on the interim analysis at Week 168 on the secondary efficacy endpoint of SVR24 was reported or identified.

The decision as to which protocol deviations should be considered as reason for exclusion from the PP 168W set should be made at the Week 168 DRM using data collected up to FU-24 which is associated with time of secondary efficacy endpoint of SVR24, and documented in the DRM report.

Analysis on the per-protocol analysis sets will be based on the actual treatment (*i.e.* subjects will be analysed 'as treated').

7.2.4 Protocol deviations leading to exclusion from the PP set

The following deviation is considered as deviation leading to exclusion from PP 24W set:

- Assessment missing or performed outside of ±14 days from the planned visit for the efficacy variable of combined response at Week 24.

The following deviation is considered as deviation leading to exclusion from PP set:

- Assessment missing or performed outside of ±14 days from the planned visit for the primary efficacy variable (Week 48).

The following deviation is considered as deviation leading to exclusion from PP 168W set:

- Assessment missing or performed outside of ±14 days from the planned visit for the secondary efficacy variable of SVR24 (Week 168).

Additional deviations leading to exclusion from the PP 24W set, PP set and PP 168W set will be documented in the clean file report.

7.2.5 Safety Analysis Set

All patients randomized to delayed treatment arm or randomized to bulevirtide and received bulevirtide at least once after randomization.
Analysis on the safety population will be based on the actual treatment (*i.e.* subjects will be analysed 'as treated').

7.3 Disposition of Subjects

The following will be presented, by country, study site, and in total:

- Number of screened subjects, in total across all treatment groups.
- Number of screening failures, in total across all treatment groups.
- Number of randomised subjects, by treatment group and in total.

Based on the number of randomised subjects, the following will also be presented by country, study site and in total, broken down by treatment group and in total across all treatment groups:

- Number and percentage of subjects who did not receive any dose of IMP.
- Number and percentage of subjects who received at least one dose of IMP.
- Number and percentage of subjects who completed the study. [Final/Follow up period]
- Number and percentage of subjects who completed Week 24/48/96/144. [Respective planned analysis]
- Number and percentage of subjects who withdrew prematurely from the study.
- Number and percentage of subjects in each of the analysis sets

In addition, a frequency table on the primary reason for premature withdrawal from the study will be presented by treatment group and in total. Percentages for this table will be based on the number of prematurely withdrawn subjects.

The number of subjects attending each study visit will also be summarised.

7.4 Protocol Deviations

An overview tables of all protocol deviations at each milestone analysis will be presented by treatment group for the randomised analysis set, including the number and percentage of subjects with at least one, and the total number, of the following:

- Any protocol deviation, in total and by grade (important/non-important).

- Any protocol deviation not related to COVID-19, in total and by grade.
- Any protocol deviation related to COVID-19, in total and by grade.

In addition, the incidence of important protocol deviations at each planned analysis, and the incidence of important protocol deviations related to COVID-19, will be summarised by category and type of deviation. For each category and type, the total number of deviations as well as the number and percentage of subjects with at least one deviation in that category or type will be presented.

7.5 Demographics and Baseline Characteristics

Summary statistics and frequencies on demographic data will be presented for the FAS datasets and PP set (PP 24W set for the 24w Interim analysis, PP 168W set for the Week 168 interim and final analysis).

The following data (collected at Screening and/or Randomisation) will be summarised:

- Demographics: age, sex, and race;
- Baseline anthropometrics: height, body weight, body mass index (BMI) and BMI categories ('<30 kg/m²' and '≥30 kg/m²');
- Cirrhosis status, and Child–Pugh score and class for cirrhotic subjects;
- Substance use: Smoking status, alcohol consumption status, drug abuse status, alcohol breath test, and urine drug test;
- Abdominal ultrasound;
- Serum alpha fetoprotein (AFP) test [IU/mL];
- Serology test results: HIV antibodies, HCV antibodies, HDV antibodies, HBeAg and HBeAg antibodies, and HBV DNA;
- HDV and HBV[2] genotyping;
- Baseline HDV RNA and HBV DNA levels (log-10 transformed values);
- Baseline HBsAg levels (log-10 transformed values);
- Baseline ALT levels;
- Baseline liver stiffness;
- Previous IFN therapy (number and % of subjects).

For HDV and HBV genotyping, only the main genotypes will be summarised in tables; if available, data on sub-genotypes will be presented in listings only.

7.6 Medical History and Concurrent Diseases

Medical history and concurrent diseases will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA).

For each system organ class and preferred term, the number and percentage of subjects with at least one condition in that system organ class or preferred term, and the number of events, will be presented. Medical history and concurrent diseases will be presented in separate tables, based on the safety analysis set.

Medical history is defined as events stopped prior to baseline. Concurrent diseases are defined as ongoing events and events stopped on or after baseline. For medical history and concurrent diseases, if the start and/or stop date is partially unknown, the following imputation rules will be used for the purpose of classifying the events:

	Imputed start date	Imputed end date
Unknown year	Missing	Missing
Unknown month	1 January	31 December
Unknown day	First of month	Last of month

If it is not possible to classify the condition based on the reported and/or imputed start and end dates, it will be considered as concurrent. In data listings, the dates will be presented as reported.

[2] HBV genotyping is performed at the first occasion of positive HBV DNA result, which can be post-baseline.

7.7 Prior and Concomitant Medication

Medications will be coded according to the World Health Organization (WHO) Drug Dictionary and summarized by therapeutic subgroup (ATC level 2) and preferred name.

For each therapeutic subgroup and preferred name, the number and percentage of subjects who used at least one medication of that therapeutic subgroup or preferred name will be presented. Prior and concomitant medications will be summarized in separate tables, based on the safety analysis set.

In addition, use of prior and concomitant HBV medications will be summarised in a similar way (in 2 separate tables), by preferred name. For definition of HBV medication, see section 8.2.4.If a reported medication cannot be coded with a preferred name, the lowest available higher-level dictionary term will be used instead in the summary tables. If a medication cannot be coded on a lower level than the therapeutic subgroup or the anatomical main group (ATC level 1), that medication will be presented as 'Not codable' under that therapeutic subgroup/anatomical main group.

Prior medication is defined as medication stopped prior to baseline. Concomitant medication is defined as ongoing medication or medication stopped on or after baseline. If the start and/or stop date is partially unknown, the following imputation rules will be used for the purpose of classifying the medication:

	Imputed start date	Imputed end date
Unknown year	Missing	Missing
Unknown month	1 January	31 December
Unknown day	First of month	Last of month

If it is not possible to classify a medication based on the reported and/or imputed start and end dates, it will be considered as concomitant. In data listings, the dates will be presented as reported.

7.8 Efficacy Evaluation

All analyses of efficacy variables will be performed using the full analysis set and the per-protocol (PP) set for the interim W24 analysis and the primary W48 analysis. There will be no separate PP sets defined for the exploratory interims at w96 and w144. Hence, no efficacy analyses using the PP set will be performed for the interims at W96 and W144 except for the main analyses repeated from w48 as described below. Efficacy analyses using PP 168W set will be performed for the interim W168 analysis and the final W240 analysis on secondary efficacy endpoints of SVR24, SVR48 and change from baseline in liver stiffness.

In addition, at W96, W144, W168 and W240 analysis, efficacy analyses using PP set determined at W48 primary analysis may be repeated for primary efficacy endpoint of combined response at W48, key secondary endpoint of undetectable HDV RNA at W48 and secondary endpoint of ALT normalization at W48 using the updated database to ensure the ongoing collection and data cleaning after W48 primary analysis will not have impact on the primary efficacy endpoint of combined response at W48, key secondary endpoint of undetectable HDV RNA at W48 and secondary endpoint of ALT normalization at W48.

FAS will be used as main analysis and will be repeated using the PP set as supportive analysis as described above. If the size of the randomised analysis set differs from the size of the full analysis set by more than 10%, the analysis of the primary efficacy variable will also be performed on the randomised analysis set.

In addition to the statistical hypothesis testing described in the subsections below, all descriptive summaries of efficacy data (primary, secondary[redacted] will also be presented for the subgroups based on presence of cirrhosis for both the full analysis set and the per-protocol analysis set as described above.

7.8.1 Primary Efficacy Variable

Combined response at Week 48

Combined response is defined as fulfilling both of below criteria:

1. Undetectable HDV RNA (HDV RNA < LOD) or decrease in HDV RNA by ≥ 2 $\log_{10}$ IU/ml from baseline;
2. ALT normalization.

Patients with missing assessment in HDV RNA or ALT on Week 24 or Week 48 respectively will be handled

as non-responder using the MEF approach regardless of the reason for absence, unless specified otherwise (see also paragraph 7.1.5 handling of missing data).

The proportions of subjects with combined response at Week 48 for each of bulevirtide 2 mg and bulevirtide 10 mg will be compared with the control group of delayed treatment. Fisher's exact test will be used to test the following two null hypotheses:

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

and

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

where p_O, p_{M2mg} and p_{M10mg} are the expected response rate for delayed treatment arm, bulevirtide 2 mg and bulevirtide 10 mg, respectively.

The overall significance level will be 0.05. However, the above hypotheses will also be tested at Week 24, and hence the nominal two-sided significance level will be split among the time points with 0.01 for Week 24 and 0.04 for Week 48.

In terms of a hierarchical testing procedure the second null hypothesis (H_{02} above) will not be rejected if the first null hypothesis (H_{01}) could not be rejected.

The frequencies, proportions of subjects with combined response at Week 48 will be presented by treatment group along with the p-values and confidence intervals for the comparison versus group A. Exact unconditional 96%-confidence intervals based on scores for the proportion differences will be presented, For the within group proportions, Clopper-Pearson 95%-confidence will be calculated.
The hypotheses specified above will be tested at the interim analysis at Week 24 with a significance level of 0.01 using the same methods. Exact unconditional 99%-confidence intervals based on scores for the proportion differences will be presented, For the within group proportions, Clopper-Pearson 95%-confidence will be calculated.

Due to the expected low number of responders under delayed treatment the analysis will not be stratified by cirrhosis or other covariables. However, as described above all descriptive analyses of efficacy will also be presented by presence of cirrhosis.

For the main and interim analysis of combined response on the FAS, the handling of time window deviations and imputation of missing values depends on whether the deviation is related to COVID-19, and the following rules will be applied:

- Deviations not related to COVID-19: Assessments made outside of the time window defined by ±30 days from the planned time point will be considered as missing. Missing values will be imputed using the missing equals failure approach (*i.e.,* subjects with a missing value will be considered as non-responders).
- Deviations related to COVID-19: If, due to COVID-19, the assessment is not performed at the planned visit, or if the entire visit is missing, the assessment will be considered as missing. Missing values will be imputed using the last observation carrying forward (LOCF) approach. If there is no previous non-missing post-baseline value that can be carried forward, the missing equals failure approach will be applied.

A sensitivity analysis will be performed on the FAS, where assessments made outside of the time window defined by ±30 days from the planned time point will be considered as missing, regardless of whether the time deviation is related to COVID-19. Missing values will be imputed using the missing equals failure approach.

The analysis on the PP sets will be performed on the observed cases without replacement of missing values.

7.8.2 Secondary Efficacy Variables

For the secondary efficacy variables except the key secondary variable, assessments made outside of the time window defined by ±30 days from the planned time point will be considered as missing, regardless of whether the time deviation is related to COVID-19. For FAS analysis of binary variables, missing values will be imputed using the missing equals failure approach. No imputations of missing values will be made for PP analysis or for the non-binary secondary efficacy variables

For the key secondary variable the same two steps approach as described for the primary endpoint will be applied.

7.8.2.1 Undetectable HDV RNA at Week 48 (key secondary variable)

For the proportion of patients with Undetectable HDV RNA at Week 48 a comparison between bulevirtide 2 mg and 10 mg will be performed. A two-sided Fisher's exact test will be used to test the following hypothesis:

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

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

This test will only be performed if the two null-hypotheses for the primary variable (H_{01} and H_{02} above) both have been rejected.

As for the primary analysis, the above hypotheses will also be tested at the interim analysis at Week 24 and hence the nominal two-sided significance level of 0.05 will be split among the time points with 0.01 for Week 24 and 0.04 for Week 48 respectively.

Exact unconditional confidence intervals based on scores for the proportion differences will be presented, with corresponding confidence levels of 99% for Week 24 and 96% for Week 48.

For the within group proportions, Clopper-Pearson 95%-confidence will be calculated.

All further analyses including the subsequent planned analyses as described in Section 7.1.6 will be considered explorative.

7.8.2.2 ALT normalization at Week 48

The proportions of subjects with ALT normalisation at Week 48 for each of bulevirtide 2 mg and bulevirtide 10 mg will be compared with the control group of delayed treatment using Fisher's exact test. Exact unconditional confidence intervals based on scores for the proportion differences will be presented, with corresponding confidence levels of 95%.

For the within group proportions, Clopper-Pearson 95%-confidence will be calculated.

7.8.2.3 Undetectable HDV RNA Week 24 and Week 48 after scheduled end of treatment (sustained virological response)

Undetectable HDV RNA at week 168 and 192 (i.e. 24 and 48 weeks after scheduled end of treatment) will be analysed in the same way as for ALT normalization.

7.8.2.4 Change from baseline in liver stiffness (kPa)

Change from baseline in liver stiffness (as measured by elastography) will be analysed using mixed-effects model for repeated measures (MMRM).

Change from baseline in liver stiffness will be the dependent variable, where data for all post-baseline analysis visits will be used. The model will include treatment, region, presence of cirrhosis, visit and treatment-by-visit interaction as fixed-effect factors, and baseline liver stiffness as covariate. Restricted maximum likelihood (REML) will be used. Within-patient variation will be modeled as random effect with unstructured covariance structure. Confidence intervals will be based on estimated means (least square means) and corresponding t-statistics.

The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. If the model fails to converge, the model will be fit using covariance matrices of the following order specified by a decreasing number of covariance parameters until convergence is met: heterogeneous Toeplitz, heterogeneous autoregressive, Toeplitz, and autoregressive.

SAS procedure PROC MIXED will be used for analysis.

This analysis will be performed at the Week 96 and subsequent analyses using MMRM. As the first post-baseline measurement for liver-stiffness is done at Week 48, this analysis done at the Week 48 main

7.9 Safety Evaluation

All evaluations of safety data will be performed on the safety analysis set.

7.9.1 Extent of Exposure

Exposure will be presented at each interim, i.e. at week 24, 48, 96, 168 and 144.

Exposure to bulevirtide will be presented for each of the groups (delayed treatment, bulevirtide 2mg and 10mg) separately and in total.

However, to account for duration of exposure the following will be presented
-Exposure

The delayed treatment group will be included in the presentation after week 48 (from Interim 2 to Final analysis).
Summary statistics will be presented for:

- treatment duration (weeks);
- total dose (mg);
- dose intensity (mg/week);
- compliance (%);

In addition, summary statistics for the number and proportion of missed doses will also be presented.

To account for duration of exposure, there will be separate presentations for the treatment phase up to Week 48 and the treatment phase after Week 48.

- Exposure at Week 24, Week 48, 96 and 144 (for Arm B and C only)
- Exposure after Week 48 to 96, after Week 48 to 144 (for all treatment groups)

For definition of exposure and compliance see section 8.4.

7.9.2 Adverse Events

Adverse events will be coded according to MedDRA.The analysis will focus on the treatment-emergent AEs (TEAE).

For Week 24 interim analysis and Week 48 main primary analysis, TEAE was defined as AEs which started or worsened after randomization (delayed treatment group) or after start of treatment (bulevirtide groups).

For Week 96, Week 144, Week 168 interim analyses and Week 240 final analysis, TEAE will be defined as the following:

- For groups B and C, the TEAEs are defined as one or both of the following:
  - Any AEs with an onset date on or after the study drug start date and no later than 30 days after permanent discontinuation of study drug
  - Any AEs leading to premature discontinuation of study drug BLV
- For group A, TEAE are defined as one of the following:
  - Any AEs with an onset date on or after the randomization date and no later than 30 days after permanent discontinuation of study drug if the subject switched to BLV after Week 48 visit
  - Any AEs leading to premature discontinuation of study drug BLV
  - Any AEs with an onset date on or after the randomization date and no later than the study discontinuation date, if subjects discontinued study before switching to BLV at Week 48 visit

If the start or end date of an AE is fully or partially unknown, the incomplete date will be imputed before performing analysis. The method to impute incomplete date is described in Appendix 3.

For serious adverse events with multiple reports (initial reports and one or more follow-up reports), only the record associated with the last report for the event will be considered for the summary tables and included in data listings. For non-serious adverse events, there are initial reports only and no follow-up reports.

TEAEs will be summarized by actual treatment group, the following will be presented:

- TEAEs within first 48 weeks for all groups
- TEAEs during entire treatment period for Arm B and C only
- TEAEs after switching to Bulevirtide at Week 48 – Week 144 for Arm A only
- AEs started after the end of treatment (FU period) for all arms
- TEAEs for all groups

An overview of all TEAEs will be presented, including the number and percentage of subjects with at least one, and the total number, of the following:

1. TEAEs;
2. Serious TEAEs;
3. TEAEs leading to withdrawal of the study medication or dose reduction;
4. Fatal TEAEs;
5. TEAEs, broken down by severity;
6. TEAEs, broken down by causality to bulevirtide (Reasonable possibility, No reasonable possibility and Not applicable)
7. TEAEs, broken down by causality to study procedure (Yes, No)

The incidence of TEAEs will be presented by system organ class and preferred term. For each system organ class and preferred term, the total number of TEAEs as well as the number and percentage of subjects with at least one TEAEs in that system organ class or preferred term will be presented. The incidence of serious TEAEs will be presented in the same way. AEs will also be presented in this way for the subgroup of ADA positive subjects and the subgroup of ADA negative subjects.

Separate tables for the incidence of TEAEs broken down by severity using the NCI-CTCAE grades used in the eCRF (Mild, Moderate, Severe, Life-threatening/ disabling and death)
and the incidence of TEAEs broken down by causality assessment (Reasonable possibility, No reasonable possibility) will also be presented by system organ class and preferred term.

There will also be tables on the most frequently reported TEAEs, on system organ class level and on preferred term level. The decision on the frequency cut-off for these tables will be taken during the analysis of the TEAE data in consultation with the author of the clinical study report and could be influenced by factors such as the overall number of TEAEs, study design, and the nature of the indication. The frequency cut-off will be mentioned in a table note.

7.9.3 Laboratory

Summary statistics on the test results and change from baseline and percent change from baseline, and shift tables on the categorisation of values in relation to the normal range, will be presented by visit for the parameters below.

For laboratory parameters with qualitative results for some subjects and quantitative results for other subjects, the quantitative (numeric) test results will be categorised as 'positive' to allow frequency tables to be presented for such parameters as well.

Qualitative test results equal to one or more plus signs ('+', '++', *etc.*) will be standardised as 'Positive'.

Haematology:

- White blood cell (WBC, Leukocytes) count
- White Blood Cell (Leukocytes) differentials, absolute [10^9/L] and relative [%] for: basophils, eosinophils, lymphocytes, monocytes, neutrophils;
- Haematocrit [%],
- Haemoglobin [g/dL],
- Platelets [10^9/L],
- Red blood cell (RBC) count,
- Reticulocytes (absolute10^9/L and relative ‰);

White Blood Cell differentials from manual assay will be excluded from analysis since these results are not considered valid.

Biochemistry:

- Albumin [g/L],
- Alkaline phosphatase [U/L],
- Aminotransferase (ALT) [U/L],
- Aspartate aminotransferase (AST) [U/L],
- Total bilirubin [umol/L],
- Direct bilirubin [umol/L],
- C-reactive protein (CRP) [mg/L];
- Chloride [mmol/L],
- Total cholesterol [mmol/L],
- Creatinine [umol/L],
- Gamma glutamyl transferase (GGT) [U/L],
- Glucose [mmol/L],
- Lipase [U/L],
- Pancreatic amylase [U/L],
- Phosphate [mmol/L],
- Potassium [mmol/L],
- Total protein [g/L],
- Sodium [mmol/L],
- Urea [mmol/L];

Blood bile salts

- total bile salts [umol/L];

Coagulogram:

- Prothrombin time [%];
- Activated partial thromboplastin time [aPTT] [sec];
- International normalised ratio (INR).

Urinalysis:

- pH
- Specific gravity
- Protein
- Glucose
- Bilirubin
- Urobilinogen
- Ketones
- Erythrocytes
- Leukocytes
- Nitrites

Vitamin D (ng/mL)

7.9.4 Physical Examination

Physical examination data will be summarised by visit (Baseline, week 24, week 48, week 96, and week 144) for each of the examined body systems below as the number and percentage of subjects with normal/ abnormal findings.

1. General appearance
2. Skin
3. Head – Eyes – Ears – Nose - Throat,
4. Lymph nodes
5. Respiratory system
6. Cardiovascular system
7. Gastrointestinal system
8. Musculoskeletal system
9. Endocrine system
10. Nervous system
11. Urogenital system

The shift from baseline will also be presented.

For each type of local site reaction, the number and percentage of subjects for whom that type of reaction was reported at at least one visit will be presented, broken down by maximum severity grade of the reaction

7.9.5 Vital Signs

Summary statistics for below vital sign parameters will be presented by visit.

1. body weight
2. BMI
3. heart rate
4. respiration rate
5. body temperature
6. blood pressure (systolic and diastolic)

For post-baseline visits, the change from baseline and percent change from baseline will also be summarised.

7.9.6 Electrocardiogram

A frequency table on the overall evaluation (assessment of normality) of electrocardiogram (ECG) will be presented by visit. For post-baseline visits, the shift from baseline will also be presented.

For all quantitative ECG parameters, summary statistics will be presented by visit. Summary statistics for the change from baseline and percent change from baseline will also be presented.

For QTc, cut-off values of 30 and 60 ms will be considered for the change from baseline, and for each cut-off value the number and percentage of subjects who experienced a change from baseline greater than the cut-

Bulevirtide plasma concentrations, summary statistics (including the geometric mean, and the arithmetic and geometric coefficients of variation [CV%]) will be presented by visit.

As the delayed treatment group (Arm A) does not start treatment until week 48, PK before and after week 48 will be presented separately as follows:

a) Plasma concentrations of bulevirtide during first 48 weeks for Arm B and C only;

b) Plasma concentrations after 48 weeks for all groups.

7.12 Evaluation of Other Variables

The presentation of other variables will be performed on the full analysis set.

7.12.1 NTCP polymorphism

Analysis details for NTCP polymorphism will be described in virology analysis plan and virology study report.

7.12.3 HBeAg

HBeAg status and HBeAg antibodies status at baseline and Weeks 48, 96 and 144 will be summarised descriptively by visit, for subjects with positive HBeAg status at Screening

7.12.4 Liver Biopsy

Descriptive statistics for the following molecular analysis and gene expression parameters will be presented based on log-10 transformed data, including the change from baseline for the transformed data:

- Molecular analysis:
  - relative expression level of HDV RNA;
  - relative expression level of HDV RNA (S region);
  - relative expression level of total HBV RNA (X region);
  - relative expression level of pregenomic HBV RNA;
  - HBV DNA (S region) [copies/cell];
  - total HBV DNA (X region) [copies/cell];
  - HBsAg.

- Molecular analysis using immunofluorescence staining:
  - HDAg, % of positive hepatocytes.
- Gene expression:
  - relative expression level of NTCP mRNA;
  - relative expression level of CYP7A1 mRNA;
  - relative expression level of CXCL10 mRNA;
  - relative expression level of ISG15 mRNA;
  - relative expression level of MX1 mRNA;
  - relative expression level of OAS mRNA;
  - relative expression level of HLA-E mRNA;
  - relative expression level of TAP1 mRNA;
  - relative expression level of USP18 mRNA;
  - relative expression level of CXCL11 mRNA;
  - relative expression level of CXCL9 mRNA;
  - relative expression level of CXCR3 mRNA;
  - relative expression level of CCL5 mRNA;
  - relative expression level of CXCL8 mRNA;
  - relative expression level of IL18 mRNA;
  - relative expression level of TGFB1 mRNA.

Data will be summarised only for subjects with available data at both visits.

The following parameters will be presented in listings only:

- Molecular analysis: DNA content [ng/µL], RNA content [ng/µL], Beta globin [copies], cccDNA [copies/ cell].
- Gene expression: GAPDH CT, RPL30CT, SERPINA1 mRNA CT.

7.13 Changes to Planned Analysis

7.13.1 Definition of the Per-Protocol Analysis

According to the clinical study protocol, the per-protocol analysis set was defined as “all patients of the FAS without any major protocol deviations”.

However, in the SAP version 2.0 and 3.0 this was modified to the following:

The per-protocol set (PP) is defined as all subjects of the full analysis set for whom no protocol deviation judged as having an impact on the primary efficacy analysis was reported or identified.

In the clinical study protocol v5.0, the per-protocol analysis set definition was updated as “all subjects of the full analysis set for whom no protocol deviation judged as having an impact on the primary efficacy analysis was reported or identified “. In addition, in the SAP version 4.0, PP 24W set and PP 168W set definition was added.

7.13.2 ALT samples

According to the protocol, different samples were to be taken for the efficacy and safety evaluations of ALT. However, during the trial, it was discovered that the frozen samples (to be used for efficacy) were not stable at –20°C and could not be used. Thus, the ALT test results from the samples for the safety evaluation will be used for the efficacy analyses as well

8 Derived Variables

8.1 Disposition of Subjects

A screening failure is defined as a screened but not randomised subject.

8.2 Demographics and Baseline Characteristics

8.2.1 Age

Age will be computed as the integer part of the time in years between the date of birth and the date the written informed consent was signed, using the SAS function yrdif() with the basis parameter set to 'age'. For subjects for whom only the year of birth is collected, age will be computed as the difference between the year the informed consent was signed and the year of birth.

8.2.2 Body Mass Index

BMI will be computed as the body weight in kg divided by the squared height in metres.

8.2.3 Previous IFN therapy

A dichotomous variable indicating whether previous IFN therapy was used will be derived. Previous IFN therapy is defined as prior medication for which the preferred name includes the word 'interferon'.

8.2.4 Prior and concomitant HBV medication

A dichotomous variable indicating HBV medications will be derived. A medication is considered as HBV medication if CMDECOD includes any of the following terms: tenofovir, tenofovir alafenamide, tenofovir disoproxil fumarate, entecavir, adefovir, lamivudine, telbivudine (regardless of capitalisation).

8.3 Change from Baseline

Change from baseline will be computed as the difference between a post-baseline value and the corresponding baseline value. Percent change from baseline will be computed as the change from baseline divided by baseline x 100.

8.4 Exposure and Compliance

Duration of exposure in weeks, computed as the time in days from the date of the first dose to the date of the last dose plus 1 day, divided by 7 days/week. The sponsor will capture, clean and validate the missing doses which are not documented in the patient diary (hereafter referred to as "sponsor-identified missed doses"), and document these in an excel file (that should be included as an appendix to the clean file report). The information captured in this file will be incorporated into the calculation of the number of missed doses, the total dose as well as dose intensity and the rate of compliance which are based on total dose.

The bulevirtide treatment duration at week x (in weeks) will be computed based on the dates of the first and last injections up to week x.

Total dose of bulevirtide at week x (in mg) will be computed as the sum of all injected doses of bulevirtide up to week x (as reported in the patient diary, which takes patient reported missed doses into consideration) minus the sponsor-identified missed doses (number of missing doses multiplied by the planned daily dose) up to week x.

The bulevirtide dose intensity at week x (in mg/week) will be computed as the cumulative dose of bulevirtide at week x divided by the duration of exposure to bulevirtide at week x.
Compliance with bulevirtide treatment (in %) at week x will be computed as the ratio of the cumulative dose of bulevirtide to the planned total dose at week x of bulevirtide (planned daily dose multiplied by X×7 days) multiplied by 100.

For Delayed treatment, presented at Week 96 and Week 144, the planned total dose at week X of bulevirtide is calculated as planned daily dose multiplied by (X-48)×7 day.

Hence, at week 24, 48, 96 and 144 the following will be calculated:

Week x	Bulevirtide treatment duration at week x (weeks)	Total dose of bulevirtide at week x (mg)	Bulevirtide dose intensity at week x (mg/week)	Compliance with bulevirtide treatment (%) at week x
week 24	first dose to dose at week 24 (or last dose before w24)	the sum of all injected doses of bulevirtide up to week 24	total dose of bulevirtide at week 24 divided by the duration of bulevirtide at week 24	Total dose of bulevirtide at week 24 divided by For bulevirtide groups: the planned total dose at week 24 of bulevirtide (planned daily dose multiplied by 24×7 days) multiplied by 100.
week 48	first dose to dose at week 48 (or last dose before w48)	the sum of all injected doses of bulevirtide up to week 48	total dose of bulevirtide at week 48 divided by the duration of bulevirtide at week 48	Total dose of bulevirtide at week 48 divided by For bulevirtide groups: the planned total dose at week 48 of bulevirtide (planned daily dose multiplied by 48×7 days) multiplied by 100.
week 96	first dose to dose at week 96 (or last dose before w96)	the sum of all injected doses of bulevirtide up to week 96	total dose of bulevirtide at week 96 divided by the duration of bulevirtide at week 96	Total dose of bulevirtide at week 96 divided by For bulevirtide groups: the planned total dose at week 96 of bulevirtide (planned daily dose multiplied by 96×7 days) multiplied by 100. For delayed treatment: the planned total dose at week 96 of bulevirtide (planned daily dose multiplied by 48×7 days) multiplied by 100.
week 144	first dose to last dose at w144 (or last dose before w144)	the sum of all injected doses of bulevirtide up to week 144	total dose of bulevirtide at week 144 divided by the duration of bulevirtide at week 144	Total dose of bulevirtide at week 144 divided by For bulevirtide groups: the planned total dose at week 144 of bulevirtide (planned daily dose multiplied by 144×7 days) multiplied by 100. For delayed treatment: the planned total dose at week 144 of bulevirtide (planned daily dose multiplied by 96×7 days) multiplied by 100.

The number of missed doses at Week X will be computed as the expected number of doses Week X minus the number of administered doses at Week X (as reported in the patient diary) plus the number of sponsor-identified missed doses. If this results in a negative number, the number of missed doses will be set to the number of sponsor-identified missed doses, or zero (0) if there were no sponsor-identified missed doses. The expected number of bulevirtide doses will be computed as the date of Week X (or the date of premature withdrawal from the study, whichever comes first) minus the date of randomisation.

The proportion of missed doses will be computed as the ratio of the number of missed doses to the expected number of doses and expressed as a percentage.

For Delayed treatment, presented at Week 96 and Week 144, the expected number of bulevirtide doses will be computed as the date of Week X (or the date of premature withdrawal from the study, whichever comes first) minus the date of Week 48.

8.5 Efficacy variables

8.5.1 Undetectable HDV RNA

Undetectable HDV RNA is defined as HDV RNA value <LOD.

8.5.2 Combined response (primary efficacy variable)

Combined response is defined as fulfilment of both of the following two conditions simultaneously:

1. Undetectable HDV RNA (HDV RNA < LOD) or decrease in HDV RNA by ≥ 2 $\log_{10}$ IU/ml from baseline;
2. ALT normalisation.

8.5.3 Histological findings

The change from baseline will be categorised as improvement (decrease of at least 1 point), no change or worsening (increase of at least 1 point) for each of the following parameters: Knodell fibrosis score, Ishak fibrosis score, METAVIR fibrosis stage and METAVIR activity grade.
The HAI score is provided in different formats from the labs providing the test results; for Russian subjects, the actual HAI score is provided, whereas for non-Russian subject a categorised HAI score is provided. To allow data to be summarised in the same way for all subjects, the HAI score for Russian subjects will be categorised into the same categories as those reported for non-Russian subjects: “0”, “1–4”, “5–8”, “9–12”,

8.6.1 Treatment Emergent Adverse Event

Two definitions of Treatment Emergent Adverse Event (TEAE) are used in this study:

For Week 24 interim analysis and Week 48 main primary analysis, TEAE was defined as AEs which started or worsened after randomization (delayed treatment group) or after start of treatment (bulevirtide groups).

For Week 96, Week 144, Week 168 interim analyses and Week 240 final analysis, TEAE will be defined as the following:

- For groups B and C, the TEAEs are defined as one or both of the following:
    - Any AEs with an onset date/time on or after the study drug start date/time and no later than 30 days after permanent discontinuation of study drug
    - Any AEs leading to premature discontinuation of study drug BLV

- For group A, TEAE are defined as one of the following:
    - Any AEs with an onset date/time on or after the randomization date/time and no later than 30 days after permanent discontinuation of study drug if the subject switched to BLV after Week 48 visit
    - Any AEs leading to premature discontinuation of study drug BLV
    - Any AEs with an onset date/time on or after the randomization date/time and no later than the study discontinuation date, if subjects discontinued study before switching to BLV at Week 48 visit

8.6.2 Physical examination

Virologic response defined as HDV RNA decrease by at least $2\ \log_{10}$ IU/mL or undetectable HDV RNA at all post-baseline visits will be derived using observed records of HDV decrease and undetectable HDV RNA at each visit. Missing virologic response at a postbaseline visit will be imputed using MEF.

If HDV RNA decrease is missing and undetectable HDV RNA is missing at a visit, the virologic response at this visit will be missing and imputed as non-responder; if HDV decrease is missing and undetectable HDV RNA is non-responder, the virologic response at this visit will be missing and imputed as non-responder; if HDV decrease is non-responder and undetectable HDV RNA is missing, the virologic response at this visit will be missing and imputed as non-responder.

9 References

1. ICH Harmonised Tripartite Guideline for Statistical Principles for Clinical Trials E9. 1998.
2. ICH Harmonised Tripartite Guideline for Structure and Content of Clinical Trial Reports E3. 1995.
3. Clinical Study Protocol MYR 301, Version 2.0 dated 01-Feb-2019.
4. Optum, HQLQv2 Scoring Guidelines for Certified Scoring. 2016.
5. EuroQol EQ-5D-3L User Guide Version 6.0. 2018.
6. FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. September 2007.

10 Signoff

We have read this SAP for the MYR 301 study and confirm that, to the best of our knowledge, the statistical analyses to be performed in this study are accurately described.

Sponsor Representative: PPD Project Manager, Gilead Sciences, Inc

SIGNATURE AND DATE

PPD

Sponsor Representative: PPD Sr Director, Biostatistics, Gilead Sciences, Inc

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SAP Author: PPD Senior Biostatistician, LINK Medical Research AB

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11 Appendices

Appendix 1 Schedule of Assessments

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

Study phase V (Visit) / W (Week) / D (Day) Procedures [1]	Screening	144-week Treatment phase (app. 3 years)*				96-week Follow-up phase		
	SCR	V1	V2 – V7	V8	V9 – V18	V19	FU 1	FU 2-5	FU 6 / EOS
	D-28 to D-1 **	W0 / D1	*± 2 days:* W4, W8, W16, W24, W32, W40	*± 2 days:* W48	*± 2 days:* W52, W56, W64, W72, W80, W88, W96, W108, W120, W132	*± 2 days:* W144	*± 3 days:* W148	*±7 days* W156, W168, W192, W216	*±7 days* W240
Concomitant therapy	X	X	X	X	X	X	X	X	X
Randomization [9]		X							
TREATMENT DISPENSING/RETURN									
Bulevirtide [10]		X [7, 10]	X [7, 10]	X [10]	X [10]	X [10]			
Treatment compliance assessment			X[7]	X	X	X			
Patient Diary Dispensing/Review/Collection		X[7]	X[7]	X	X	X			
CCI									
LOCAL LABORATORY/STUDY SITE									
Urine pregnancy test [11]	X	X	X	X	X	X	X	X	X
Urine drug screening test	X								
ANALYSES PERFORMED IN CENTRAL LABORATORY / SAMPLES TO BE SENT TO CENTRAL LABORATORY AT ONCE									
Serology (anti-HIV, anti-HCV, anti-HDV)	X								
HCV RNA (if anti-HCV positive at SCR)	X								
CCI									
Urinalysis	X	X [6]	X [12]	X	X [12]	X		X [12]	X
Haematology [13]	X	X [6]	X	X	X	X	X	X	X
Biochemistry (full panel) [14]	X	X [6]	X (W24)	X	X (W72, W96, W120)	X			X

Study phase V (Visit) / W (Week) / D (Day) Procedures [1]	Screening	144-week Treatment phase (app. 3 years)*				96-week Follow-up phase		
	SCR	V1	V2 – V7	V8	V9 – V18	V19	FU 1	FU 2-5	FU 6 / EOS
	D-28 to D-1 **	W0 / D1	*± 2 days:* W4, W8, W16, W24, W32, W40	*± 2 days:* W48	*± 2 days:* W52, W56, W64, W72, W80, W88, W96, W108, W120, W132	*± 2 days:* W144	*± 3 days:* W148	*±7 days* W156, W168, W192, W216	*±7 days* W240
Biochemistry (abbreviated panel) [15]			X (W4, W8, W16, W32, W40)		X (W52, W56, W64, W80, W88, W108, W132)		X	X	
Coagulogram [16]	X	X [6]	X (W8, W24, W40)	X	X (W64, W80, W96, W108, W120, W132)	X		X (W168, W192, W216)	X
Total blood bile salts		X	X	X	X	X	X	X	X
Alpha-fetoprotein test	X								
Vitamin D		X	X (W24)	X	X (W72, W96, W120)	X		X (W168, W192)	X
HBV DNA for pts. not receiving Nucleoside / nucleotide analogues	X								
Serum alpha-2-macroglobulin		X		X	X (W96)	X		X (W168)	X
ANALYSIS PERFORMED IN CENTRAL VIROLOGY LABORATORY / SAMPLES TO BE SENT TO CENTRAL LABORATORY AT ONCE									
HDV RNA	X								
ANALYSIS PERFORMED IN CENTRAL VIROLOGY LABORATORY / SAMPLES TO BE STORED AT SITE									
CCI									
HDV RNA		X	X	X	X	X	X	X	X
CCI									
HBeAg and HBeAg antibodies		X		X	X (W96)	X			X

Study phase V (Visit) / W (Week) / D (Day) Procedures [1]	Screening	144-week Treatment phase (app. 3 years)*					96-week Follow-up phase		
	SCR	V1	V2 – V7	V8	V9 – V18	V19	FU 1	FU 2-5	FU 6 / EOS
	D-28 to D-1 **	W0 / D1	*± 2 days:* W4, W8, W16, W24, W32, W40	*± 2 days:* W48	*± 2 days:* W52, W56, W64, W72, W80, W88, W96, W108, W120, W132	*± 2 days:* W144	*± 3 days:* W148	*±7 days* W156, W168, W192, W216	*±7 days* W240
ANALYSIS PERFORMED IN CENTRAL LABORATORY / SAMPLES TO BE STORED AT SITE									
ALT		X	X	X	X	X	X	X	X
CCI									
NTCP polymorphism[20]		X							
CCI									
Pharmacokinetics		X [22]	X [22]	X [22]	X [22]	X [22]			
Liver biopsy	X [23]			X [24]					

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

1. Detailed description of all study procedures can be found in Section 6 of the protocol.
2. Signed and dated informed consent must be obtained before any procedure specific to the 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 patient receives currently and therapies that were discontinued within 3 months before Screening.
5. A complete physical examination is performed at Screening (SCR), Randomization (V1), Week 24, Week 48, Week 96, and Week 144. A complete physical examination includes evaluation of general appearance, skin, head, eyes, ears, nose and throat, lymph nodes, respiratory, cardiovascular, gastrointestinal including hepatobiliary assessment, musculoskeletal, endocrine system, nervous systems, and urogenital system. At all other visits, a symptom directed physical examination is performed.
6. If at Screening was done over 14 days ago.
7. Arm A: starting from W48.

8. Vital signs include body temperature, heart rate, and blood pressure. Vital signs are measured as indicated in Table 1 and when clinically indicated.
9. Patients eligible for the study are randomized after completion of all procedures scheduled for Screening and Day 1 (except study drug administration, patient diary dispensing and assessment of adverse events, sample collection for PK) and confirmation of subject's eligibility
10. Patients should be instructed NOT to administer study drug at home at days of visits to study sites. At these days study drug is administered at study site in accordance with schedule of events for assessment of immunogenicity and pharmacokinetics of the study drug.
11. Only for women of childbearing potential.
12. Urinalysis is not needed at V2 (W4), V9 (W52), and FU3 (W168).
13. Hematology includes hemoglobin, hematocrit, reticulocytes, RBC, platelet count, WBC with differential (absolute counts and percentage for neutrophils, eosinophils, basophils, monocytes, and lymphocytes).
14. Subjects must attend study sites after fasting for at least 9 hours (water and concomitant medications are permitted) for the purpose of conducting the biochemistry. Full biochemistry includes: total protein, albumin, ALT, AST, GGT, P-amylase, alkaline phosphatase, lipase, total bilirubin, direct bilirubin, total cholesterol, creatinine, urea, glucose, potassium, sodium, chloride, phosphorus, and CRP.
15. Subjects must attend study sites after fasting for at least 9 hours (water and concomitant medications are permitted) for the purpose of conducting the biochemistry. Abbreviated biochemistry includes: albumin, ALT, AST, GGT, total bilirubin, direct bilirubin, creatinine, lipase, P-amylase, CRP.
16. Coagulogram includes prothrombin time, INR and aPTT.

CCI

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

CCI

CCI

20. Blood samples for determination of NTCP polymorphism are collected at Day 1 for all the patients. NTCP polymorphism will be performed in central laboratory for patient who are either non-responders or have viral breakthrough as detailed in Section 6.4.4 of the protocol.

CCI

22. During first 48 weeks pharmacokinetics samples are taken only for Arms B and C. One sample at each visit 1h±15 min post bulevirtide dose.
23. At Screening liver biopsy is performed after confirmation of eligibility. If a liver biopsy was performed within 1 year prior to Screening, and a patient can provide biopsy records and appropriate biopsy specimens, the available specimens can be used for the baseline evaluation and biopsy at Screening is not required. Otherwise liver biopsy at screening is performed if feasible provided that patient is considered to be eligible after the review of all eligibility criteria.
24. Liver biopsy should be performed within ± 7 days from the date of the visit for patients who don't 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.

Appendix 2 Potential liver related clinical events

For each of the pre-specified potential liver related clinical events (except hospitalisation and death), the applicable MedDRA preferred terms are listed below:

- **Cirrhosis development:**
  - Hepatic cirrhosis
- **Development or worsening of jaundice:**
  - Jaundice
- **Development or worsening of coagulopathy:**
  - Coagulopathy
- **Development or worsening of ascites:**
  - Ascites
  - Bacterascites
  - Spontaneous bacterial peritonitis
- **Development or worsening of hepatic encephalopathy:**
  - Hepatic encephalopathy
  - Coma hepatic
  - Asterixis
- **Bleeding from varices:**
  - Oesophageal varices haemorrhage
  - Gastric varices haemorrhage
  - Intestinal varices haemorrhage
  - Anorectal varices haemorrhage
- **Hepatocellular carcinoma development:**
  - Hepatic cancer
  - Hepatocellular carcinoma
  - Liver carcinoma ruptured
  - Mixed hepatocellular cholangiocarcinoma
- **Liver transplantation:**
  - Liver transplant
  - Renal and liver transplant
- **Liver failure**
  - Acute hepatic failure
  - Subacute hepatic failure
  - Acute on chronic hepatic failure
  - Hepatic failure
  - Hepatorenal syndrome
  - Hepatorenal failure
  - Hepatopulmonary syndrome

Appendix 3 Imputation of incomplete AE start or end date

1 For Arms B and C

1.1 to impute partial AE date if **year and month are available**:

	Imputed start date	Imputed end date
If AE year/month same as 1st dose year/month	Same as 1st dose date or AE end date whichever comes first.	Last of the month
If AE year/month before 1st dose year/month	First of the month	Last of the month
If AE year/month after 1st dose year/month	First of the month	Last of the month

1.2 to impute partial AE date if **only year is available**:

	Imputed start month/date	Imputed end month/date
If AE year same as 1st dose year	Same as 1st dose month/date or AE end month/date whichever comes first	December 31
If AE year before 1st dose year	January 1	December 31
If AE year after 1st dose year	January 1	December 31

1.3 to impute partial AE **start** date if **neither year nor month** is available:

	Imputed AE start year/month/date
If AE end date is before 1st dose date	AE end date
If AE end date is at/after 1st dose date	Same as 1st dose date

1.4 to impute partial AE **end** date if **neither year nor month** is available:

Impute the missing AE end date using the last visit date in database for this subject, or AE start date, whichever comes last.

2 for Arm A (i.e., delayed treatment)

2.1 to impute partial AE date if **year and month are available**:

	Imputed start date	Imputed end date
If AE year/month before randomization year/month	First of the month	Last of the month
If AE year/month same as randomization year/month	Same as randomization date or AE end date whichever comes first.	Last of the month
If AE year/month after randomization year/month but before 1st BLV dose year/month	First of the month	Last of the month
If AE year/month at 1st BLV dose year/month	1) if Relationship to bulevirtide='not applicable (bulevirtide not administred)', then first of the month 2) if Relationship to bulevirtide **not** equal to 'not applicable (bulevirtide not administred)', then same as 1st BLV dose date or AE end date whichever comes first.	Last of the month
If AE year/month after 1st BLV dose year/month	First of the month	Last of the month

2.2 to impute partial AE date if **only year is available**:

	Imputed start month/date	Imputed end month/date
If AE year before randomization year	January 1	December 31
If AE year same as randomization year and before 1st BLV dose year (randomization year < 1st BLV year)	Same as randomization month/date or AE end month/date whichever comes first	December 31
If AE year same as 1st BLV dose year (randomization year = 1st BLV year)	1) if Relationship to bulevirtide='not applicable (bulevirtide not administred)', then same as randomization month/date or AE end month/date whichever comes first. 2) if Relationship to bulevirtide **not** equal to 'not applicable (bulevirtide not administred)', then same as 1st BLV dose month/date or AE end month/date whichever comes first.	December 31
If AE year same as 1st BLV dose year (randomization year < 1st BLV year)	1) if Relationship to bulevirtide='not applicable (bulevirtide not administred)', then January 1. 2) if Relationship to bulevirtide **not** equal to 'not applicable (bulevirtide not administred)', then same as 1st BLV dose month/date or AE end month/date whichever comes first.	December 31
If AE year after 1st BLV dose year	January 1	December 31

2.3 to impute partial AE **start** date if **neither year nor month** is available:

	Imputed AE start year/month/date
If AE end date is before randomization date	AE end date.
If AE end date is at/after randomization date but before 1st BLV dose date	Same as randomization date
If AE end date is at/after 1st BLV dose date	if Relationship to bulevirtide='not applicable (bulevirtide not administred)', then same as Randomization date. 2) if Relationship to bulevirtide **not** equal to 'not applicable (bulevirtide not administred)', then same as 1st BLV dose date.

2.4 to impute partial AE **end** date if **neither year nor month** is available**:**

Impute the missing AE end date using the last visit date in database for this subject, or AE start date, whichever comes last.

Verification

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