Clinical Research and Development

LDT600 (Telbivudine, Sebivo®/Tyzeka®)

Clinical Trial Protocol CLDT600A2306 / NCT02058108

A randomized, double-blind, 104-weeks treatment study to evaluate the efficacy, safety, tolerability and pharmacokinetics of telbivudine oral solution and tablets in children and adolescents with compensated HBeAg-positive and negative chronic hepatitis B virus infection

Phase III

RAP Module 3 – Detailed Statistical Methodology

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Amendment 2 v1 draft	05Jul2017	Updates transpiring after the review of the dry 1 TLFs.
Amendment 2 v2 draft	22Sep2017	Further feedback from the clinical team

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List of abbreviations

AASLD	American Association of the Study of Liver Diseases
ADR	Adverse Drug Reaction
ADV	Adefovir
AE	adverse event
AESI	adverse event of special interest
Alb	albumin
ALT	alanine aminotransferase
AFP	alpha-fetoprotein
AST	aspartate aminotransferase
ALP	alkaline phosphatase
b.i.d.	twice a day
CFR	US Code of Federal Regulations
CHB	Chronic Hepatitis B
CK	Creatine Kinase
CMV	Cytomegalovirus
CRF	Case Report/Record Form (paper or electronic)
CPO	Country Pharma Organization
CRO	Contract Research Organization
CTP	Child-Turcotte-Pugh
DNA	Deoxyribonucleic acid
DS&E	Drug Safety & Epidemiology
EASL	European Association for the Study of the liver
EBV	Epstein-Barr virus
ECG	Electrocardiogram
EDC	Electronic Data Capture
ETV	Entecavir
eGFR	estimated Glomerular Filtration Rate
EMG	Electromyography
FAS	full analysis set
GCP	Good Clinical Practice
HAV	Hepatitis A virus

HBeAb	Hepatitis Be antibody
HBeAg	Hepatitis Be antigen
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCG (β-HCG)	β-human Chorionic Gonadotropin
HCV	Hepatitis C virus
HDV	Hepatitis D virus
HEV	Hepatitis E virus
HIV	Human immunodeficiency virus type 1 and type 2
HSV	Herpes Simplex virus
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IFN	Interferon
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Randomization Technology
i.v.	intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LAM	Lamivudine
LDT (LdT)	Telbivudine
LOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
NLA	National Lipid Association
NSAID	Non-steroidal Anti-Inflammatory Drug
o.d.	once a day
PCR	Polymerase Chain Reaction
PNR	Primary Non-Response
PK	Pharmacokinetic

p.o.	oral
PPS	per protocol set
PT	Prothrombin time
PTY	Patient treatment years
q.d.	quaque die (daily)
SAE	serious adverse event
SUSAR	Suspected Unexpected Serious Adverse Reactions
SPC	Summary of Product Characteristic
TB / TBil	total bilirubin
TDF	Tenofovir Disiproxil Fumarate
ULN	Upper Limit of Normal
VB	Virological breakthrough
WBC	White Blood cells
WHO	World Health Organization

1 Introduction

1.1 Study design

This protocol will enroll HBeAg positive and HBeAg negative patients into the randomized, double-blind and placebo-controlled, 104-weeks treatment study. A screening period of 6 weeks will be used to assess patient eligibility. Patients will be treated for a total of 104 weeks and will have a 12-weeks safety follow-up period.

Patients will be stratified by 1) age group and 2) HBV DNA level. Approximately 80% of patients with lower HBV DNA at screening (i.e. for HBeAg positive patients HBV DNA <9 $\log_{10}$ and HBeAg negative patients with HBV DNA <7 $\log_{10}$ copies/mL) are expected to be recruited.

Subsets of patients by age (calculated based on birthday at randomization visit (baseline: day1)) are defined as:

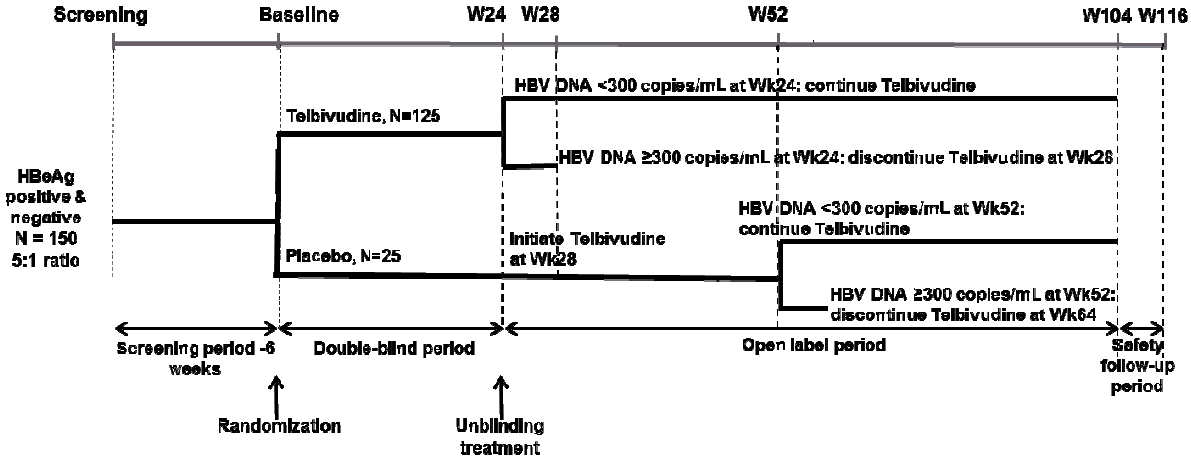
- Age group 1: from 2 to less than 6 years old
- Age group 2: from 6 to less than 12 years old
- Age group 3: from 12 to less than 18 years old

At Baseline (visit 2), eligible patients will be randomized in a double blind method to telbivudine or placebo in a ratio 5:1. The total double-blind period will be 24 weeks.

At Week 24 (visit 6), treatment will be unblinded:

- patients receiving telbivudine with HBV DNA <300 copies/mL (51 IU/mL) at Week 24 (visit 6) will remain on telbivudine treatment until Week 104 (visit 13);
- patients on telbivudine treatment with confirmed HBV DNA ≥300 copies/mL (51 IU/mL) at Week 24 (visit 6) will be discontinued from study drug at the next visit (Week 28).
- for patients on placebo, eligibility will be checked at Week 24 (visit 6):
    - Patients with confirmed eligibility will initiate treatment with telbivudine at Week 28 (visit 7). After 24 weeks on telbivudine treatment (Week 52 (visit 9), HBV DNA level will be assessed. Patients with HBV DNA <300 copies/mL (51 IU/mL) will remain on treatment until last on-treatment study visit (Week 104 (visit 13)); patients with HBV DNA ≥300 copies/mL (51 IU/mL) will be discontinued from the study at Week 52 (visit 9).
    - Placebo patients not eligible for telbivudine treatment at Week 28 (visit 7) may continue in the study until Week 52 (visit 9) and may start telbivudine treatment at a later visit until Week 52 (visit 9) based on investigator's decision and patient agreement

Patients with confirmed complete response (defined as HBV DNA <300 copies/mL (51 IU/mL), HBeAg seroconversion and ALT normalization) will continue telbivudine treatment for another 52 weeks from the day of confirmation. At the end of this "consolidation period", if the complete response is maintained, patients could be considered for discontinuation of telbivudine at the discretion of the investigators and remain in the study to monitor off-treatment efficacy and safety.



On Jan 6, 2017, patient recruitment and randomization was placed on temporary hold and an interim analysis for futility was requested by the Data Monitoring Committee. Following DMC review of the interim analysis and a recommendation by the DMC to stop the study, Novartis made a decision to terminate the study. At that time, 53 patients had been randomized into the study.

1.2 Objectives

Primary objective:

The primary objective of this study is to demonstrate the antiviral efficacy of telbivudine compared to placebo in pediatric patients by determining the percentage of patients achieving serum HBV DNA level of <300 copies/mL (51 IU/mL) at Week 24.

Secondary objectives:

The secondary objectives of this study are:

1. To assess the antiviral efficacy as evaluated by:
    a. Proportion of patients achieving HBV DNA <300 copies/mL (51 IU/mL) at Week 52 and Week 104
    b. Proportion of patients achieving HBV DNA < Lower Limit of Quantification (LLOQ) (< LLOQ defined as undetectable HBV DNA, ≥ LLOQ defined as detectable HBV DNA), <1000 copies/ml (or 200 IU/mL), <10,000 copies/ml (or 2 000 IU/mL) and ≥10,000 copies/mL (or 2 000 IU/mL) at Week 24, 52 and 104
    c. Serum HBV DNA reduction from baseline
    d. Time to achieve HBV DNA <300 copies/mL (51 IU/mL)
    e. Proportion of patients with Primary non-response
2. To assess the biochemical response at Week 24, 52 and 104 as evaluated by proportion of patients whose baseline ALTs were abnormal (defined as ALT >1 x Upper Limit of Normal [ULN]) and subsequently normalized
3. To assess the serological responses at Week 24, 52 and 104 as evaluated by:

   a. Proportion of HBeAg positive patients at baseline who subsequently have HBeAg loss and HBeAg seroconversion (defined as loss of HBeAg with detectable HBeAb)
   b. Proportion of HBsAg positive patients at baseline who subsequently have HBsAg loss and HBsAg seroconversion (defined as loss of HBsAg with detectable HBsAb)
4. To assess the percentage of patients achieving composite endpoints at Week 52 and 104:
   a. HBV DNA <300 copies/mL (51 IU/mL), ALT normalization and HBeAg seroconversion for HBeAg positive patients only
   b. HBV DNA <300 copies/mL (51 IU/mL) and ALT normalization for HBeAg negative patients.
5. To assess virological breakthrough (VB) as evaluated by:
   a. Cumulative rate of patients with confirmed VB at Week 52 and 104
   b. Time to VB
6. To assess the presence of treatment emergent genotypic resistance associated with virological breakthrough over the study period, or in patients with HBV DNA≥300 copies/mL (51 IU/mL) at Week 24 and discontinued from the study treatment (or at discontinuation if prior to Week 24 for subjects with at least 16 weeks of LDT treatment)
7. To evaluate the safety and tolerability of telbivudine at Week 52 and 104 defined by AEs, SAEs, adverse events of special interest (AESI) (including muscle related events) and death; laboratory evaluations specifically on-treatment and post-treatment ALT flares, incidence and clinical significance of CK elevations; growth and development (linear growth and sexual maturation); development of liver decompensation and/or HCC.

Due to early termination of the trial, objectives related to Week 52 and Week 104 will not be addressed.

2 Statistical methods

2.1 General

2.1.1 Statistical considerations

SAS version 9.3 or later will be used in all analyses.

All confidence intervals will be based on 2-sided 95% confidence intervals, unless otherwise specified.

The total patient accrual in this study is expected to be 150 patients.

Summary statistics will include the mean, standard deviation, median, minimum, and maximum values for continuous variables, and frequencies and percentages in each category (including a category labeled as 'missing' when appropriate) for categorical variables.

The primary analysis will be done at Week 24. As the study is being terminated, and only 2-3 patients are anticipated to reach 52 weeks of treatment with telbivudine, no formal analysis will be performed beyond week 24.

The following treatment grouping will be used for all efficacy and safety analyses:

- **Initial LdT**: patients initially treated with Telbivudine.
- **Initial Placebo**: patients initially treated with Placebo.
- **Overall**: patients from both groups.

2.1.2 Baseline definition

Baseline will be defined as the last available assessment, from scheduled or unscheduled visit, prior to the first dose of study drug.

2.1.3 Efficacy censoring date

A patient's censoring date is the date of the first occurrence of: two days after the last dose of the study drug, the start date of first prohibited Hep-B related medication, pregnancy date (if any) and any protocol deviation with codes C01, C02, all codes starting with D, M01, M02, S05, as defined in Appendix 3: Protocol Deviations.

2.1.4 On-treatment definition

On-treatment for all summaries except adverse events will be defined as any assessment after the first dose of the study drug up to and including one day after the last dose of the study drug.

For adverse events summaries 30 days will be added to the end of the on-treatment period definition.

2.1.5 Handling of missing data

All efficacy observations on or after censoring date will be treated as missing.

To assess the robustness of the results due to missing data, the analysis of primary and all secondary efficacy endpoints will be performed based on two analysis populations.

- Full Analysis Set (FAS) population with imputation. In this analysis, the missing data will be imputed as described below in section 2.7.1;
- Per Protocol Set analysis with observed data only. Missing data will not be imputed for this analysis, except in the following case: patients with confirmed complete response who discontinue due to satisfied efficacy will have their response prior to discontinuation carried forward to all subsequent scheduled visits.

Statistical comparisons of GFR between the treatment groups or between baseline and post-baseline visits will be performed in two ways:

- Missing GFR assessments imputed using the LOCF method, i.e. carrying forward the last available post-baseline observation up to Week 24.
- Missing GFR assessments not imputed.

In other GFR summaries missing assessments will not be imputed.

HBV DNA assay results below the lower limit of detection (LLD, 1.30 log IU/mL) of the assay of laboratory performing the test will be assigned a value equal to one half of the LLD for the statistical analyses and tabulations.

2.2 Visit windows

Assessments will be generally assigned to study weeks based on the nominal visit week number. However, assessments from early termination visits will be assigned to the next scheduled visit after the last scheduled visit that the subject has attended prior to early termination.

Unscheduled visits generally will not be used in by-visit summaries. However, unscheduled visits will be used in the following situations:

- If a patient does not have a scheduled assessment at a particular visit, but has an unscheduled assessment within +/- 7 days of the scheduled visit date, this unscheduled assessment will be used for this visit in by-visit summaries. In case multiple unscheduled assessment exist within the window, the one closest to the scheduled visit date will be used. In case two equidistant unscheduled visit exist, one before and one after the scheduled visit date, the earlier one will be used.
- As mentioned in the baseline definition, unscheduled visits will be considered for the selection of baseline assessment.

2.3 Analysis set

2.3.1 Randomized set

The randomized set will be defined as all subjects who were randomized. Unless otherwise specified, mis-randomized subjects (mis-randomized in IRT) will be excluded from the randomized set. (Mis-randomized subjects are defined as cases where IRT contacts were made by the site either prematurely or inappropriately prior to confirmation of the subject's final randomization eligibility and double-blind medication was not administered to the subject).

2.3.2 Safety set

The Safety set will consist of all subjects who received at least one dose of study drug during the treatment period. Subjects will be analyzed according to treatment received. All safety analysis will be done on the safety set.

2.3.3 Full Analysis Set (FAS)

The FAS will be comprised of all subjects from the randomized set to whom study treatment has been assigned. Following the intent-to-treat principle, subjects will be analyzed according to the treatment assigned to at randomization. If the actual stratum is different to the assigned stratum in IRT, the actual stratum will be used in analyses. The FAS is the primary efficacy analysis set.

2.3.4 Per-protocol set (PPS)

The PPS will be defined as a subset of FAS who do not have major protocol deviations, as shown in the table below

2.3.5 Protocol deviations leading to exclusion from populations

Protocol deviations defined in the Appendix 3: Protocol Deviations that lead to patient classification into the analysis set as follows:

Analysis Set	PD criteria which leads patient to be excluded (PD group codes)	Non-PD criteria which leads patient to be excluded
Randomized	None	Patient is not randomized
Safety	None	Patient did not take study drug
FAS	None	Patient is not randomized
PPS	All inclusion/exclusion criteria (codes starting with I and E), S02	Patient is not randomized

All exceptional cases and problems and the final decisions on the allocation of patients to populations will be fully defined and documented before database lock (in particular before breaking the blind where applicable) and will be fully identified and summarized in the clinical study report according to ICH E9.

2.4 Disposition, demographics, background characteristics and analysis populations

Disposition

The number and percentage of patients in the following subsets will be summarized by treatment group:

- randomized
- completing Week 24 visit
- completing the treatment period per CRF
- completing the study (with follow-up period) per CRF
- discontinuing the treatment period or the study with reasons of discontinuation.

For patients in the Initial Placebo treatment group the number and percentage of patients switching and not switching to LdT after Week 24 will be presented along with the reasons for not switching.

All disposition information will be listed.

The number and percentage of patients with protocol deviations will be summarized by treatment arm and also presented in a data listing.

Analysis populations

The number and percentage of patients included in each population will be summarized by treatment group. Data listing will also be presented.

Demographics and baseline characteristics

The following demographic variables and baseline disease characteristics will be summarized by treatment group.

Demographic variables

Continuous variables:

- Age (years)

Age will be calculated as the number of whole years from the patient's date of birth to the date of baseline visit.

Categorical variables:

- Age group (2 - <6, 6 - <12, 12-<18 years)
- Sex (male, female)
- Predominant race (Caucasian, Black, Asian, Native American, Pacific Islander, Other)
- Ethnicity (Hispanic/Latino, Chinese, Indian (Indian subcontinent), Japanese, Mixed Ethnicity, Other)
- Source of subject referral.
- Geographic region (Asia, Europe)
- Country

Baseline characteristics

Continuous variables:

- Weight (kg)
- Height (cm)
- BMI

- HBV DNA (log_{10} copies/mL)
- ALT (IU/L)
- AST (IU/L)
- CK (IU/L)
- Glomerular filtration rate by Schwarz formula
- Liver stiffness measurement by FibroScan (if available).

Categorical variables:

- [redacted]
- [redacted]
- ALT – multiples of ULN (<1x, 1x-<2x, 2x-<5x, 5x or more, Missing)
- AST - multiples of ULN (<1x, 1x-<2x, 2x-<5x, 5x or more, Missing)
- CK - multiples of ULN (Grade 0: ≤1x; Grade 1: >1x - ≤3x, Grade 2: >3x - ≤7x, Grade 3: >7x - ≤10x, Grade 4: 10x or more, Missing)
- HBV DNA (log_{10} copies/mL) (low, defined as < 9 log for HBeAg-positive patients and < 7 log for HBeAg negative vs. high, defined as >= 9 log for HbeAg-positive patients and >= 7 log for HBeAg negative).

Mean, median, standard deviation, minimum and maximum values will be presented for continuous variables by treatment group. The number and percentage of patients in each category for categorical variables will be presented by treatment group.

This summary will be performed for all patients in the safety set and also separately for HBeAg positive and HBeAg negative.

Hepatitis B related medical history

The following characteristics will be summarized in a frequency table by treatment group:

- If the patient was treated before for Hepatitis B
- If treated, which prior treatments were taken (Common IFN, Peg-IFN, Lamivudine, Entecavir, Adefovir, Tenofovir or other); patients will count in all applicable categories.
- Probable route of HBV acquisition (Mother known to be HBV carrier, Other family member(s) known to be HBV carrier(s), History of other parenteral exposure(s), Other risk factor(s) or Unknown); patients will count in all applicable categories.

Medical history

General medical history will be coded to MedDRA (version 19.1) and summarized by treatment group, system organ class and preferred term.

2.5 Study medication

2.5.1 Exposure

Study drug administration information will be included in data listings.

Duration of exposure to each of the study drugs (Telbivudine or Placebo) will be summarized separately. For patients who switched from Placebo to Telbivudine both durations will be summarized separately.

Duration of exposure to Telbivudine or Placebo will be defined as the number of weeks from the day of the first dose of the drug to the day of the last dose of the drug.

For the exposure summary descriptive statistics for the duration of exposure will be presented.

For each patient, time-weighted average dose will be calculated. It will be defined as follows:

[Sum of (Total Daily Dose (mg) / Patients' weight (kg) * (End date of Dose – Start date of Dose + 1) taken over all patient's doses] / [Total duration of exposure (days)]

Time-weighted average dose will be summarized descriptively by treatment groups for LdT treatment only.

The analysis will be performed for the safety set. Data listing will also be provided.

Expected daily dose (mg) will be calculated for each patient as follows:

- If subject weight is < 30 kg: as 20mg * weight (kg)
- If subject weight is >= 30 kg: 600 mg

This calculated daily dose will be compared with actual daily dose. A listing of subjects with actual daily dose that differs from the expected daily dose by more than 10% of the expected daily dose will be provided.

2.5.2 Compliance

Compliance will be assessed by the investigator and/or study personnel at each visit using the pill counts or volume solution evaluation and some specific questions raised to the patient to assess the compliance.

The investigator will record the percentage of compliance between visits in the case record form (CRF), using the pill count, the volume solution evaluation, the answers provided by the patients on specific compliance questions and his/her experience with the patient.

There are three categories of compliance:

- Good compliance equals ≥ 90%
- Fair compliance equals between 70% – 89%
- Poor compliance equals < 70%

Compliance will be summarized based on investigator’s rating (poor, fair or good) by all nominal visits in the study using FAS.

2.6 Prohibited medications

Prohibited medications will be coded using the WHO Drug Reference List that employs the Anatomical Therapeutic Chemical classification system.

Efficacy data will be censored after the start date of first use Hepatitis B related medications other than protocol-assigned Telbivudine.

Summary tables will be provided presenting the number and percentage of patients receiving the prohibited medications after the start of study drug administration, by ATC class and preferred term.

2.7 Efficacy evaluation

2.7.1 Efficacy endpoints and analysis populations

The following endpoints are defined by the protocol and will be used for efficacy evaluation.

- **Primary efficacy endpoint**: rate of HBV DNA < 300 copies/mL (51 IU/mL) at week 24.
- **Secondary efficacy endpoints:**
  - rate of HBV DNA < low limit of detection at Week 24;
  - rate of HBV DNA < 1000 copies/mL and < 10000 copies/mL at Week 24
  - Serum HBV DNA reduction from baseline
  - Time to achieve HBV DNA <300 copies/mL (51 IU/mL)
  - Proportion of patients with Primary non-response
  - Proportion of patients with ALT normalization at Week 24among those with abnormal ALT at baseline.
  - Serum ALT and its change from baseline.
  - Proportion of HBeAg positive patients at baseline who subsequently have HBeAg loss and HBeAg seroconversion at Week 24.
  - Proportion of HBsAg positive patients at baseline who subsequently have HBsAg loss and HBsAg seroconversion at Week 24.
  - Composite endpoint: HBV DNA <300 copies/mL (51 IU/mL), ALT normalization and HBeAg seroconversion for HBeAg positive patients only at Week 24Composite endpoint: HBV DNA <300 copies/mL (51 IU/mL) and ALT normalization for HBeAg negative patients at Week 24
  - Cumulative rate of patients with confirmed Virologic Breakthrough (VB) at Weeks 24.
  - Time to initial Virologic Breakthrough.
  - Proportion of patients with cumulative treatment emergent genotypic resistance at Weeks 24.

All efficacy endpoints will be analyzed for FAS and PPS populations. In the FAS analysis the following method will be used to impute missing values. If no assessment, scheduled or unscheduled, is available within a particular visit window, then the value from the available visit closest in time to the scheduled date of the missing visit will be used to impute the value

for this visit. In case of equal distances from the scheduled visit date, the earlier measurement will be used.

The analysis for Per Protocol Set will be performed on observed values without any imputation, except in the following case: patients with confirmed complete response who discontinue due to satisfied efficacy will have their response prior to discontinuation carried forward to all subsequent scheduled visits.

The main analysis will be for the FAS population with the above imputation rules. PPS analysis will be supportive.

2.7.2 Efficacy endpoints definitions

When deriving all following efficacy endpoints, all efficacy observations on or after the censoring date (section 2.1) will be treated as missing.

HBV DNA < 300 copies/mL:

Serum HBV DNA < 300 copies/mL.

HBV DNA < LLOQ (PCR Negativity):
Serum HBV DNA < 169 copies/mL, the low limit of quantification (LLOQ) of the COBAS TaqMan HBV Test that is used in this study.

HBV DNA < 1000 copies/mL, HBV DNA < 10000 copies/mL:

Serum HBV DNA < 1000 copies/mL (3log) or < 10000 copies.mL (4 log).

ALT normalization:

ALT normalization is defined as ALT within normal limits on two successive visits for a patient with an elevated ALT (> 1.0 × ULN) at the baseline. Relative to the two successive visits, a visit can be scheduled or unscheduled and missing values are not considered in determining if a patient has ALT normalization.

Hence, for a particular visit, a patient is considered to have ALT normalization if the patient's ALT value at that visit and either the previous or subsequent ALT value are ≤ 1.0 ULN and the patient's baseline ALT is elevated (> 1.0 × ULN). If a patient's last ALT value is ≤ 1.0 × ULN the patient will be defined as having ALT normalization at that time-point. The "last visit" is defined as the last visit occurring prior to the patient's censoring date.

In patients with baseline ALT <= 1.0 X ULN, this endpoint is not defined.

1 log above Nadir virologic breakthrough

1 log above nadir virologic breakthrough is defined as a confirmed (i.e. on two consecutive visits or on the last on-treatment visit) HBV DNA increase of >=1 $\log_{10}$ copies/mL above nadir HBV DNA (the lowest post baseline HBV DNA level achieved) *or* HBV DNA ≥ 300 copies/mL (51 IU/mL) after initial response with HBV DNA < 300 copies/mL (51 IU/mL). Note: the protocol specifies that the two consecutive visits when the patient's HBV DNA is 1 log above nadir have to occur within 4 weeks interval, as this reflects clinical practice. However, no time restriction on these two visits will be placed in the analysis.

Cumulative virologic breakthrough

A patient is defined to have a cumulative virologic breakthrough at a visit if the patient had 1 log above nadir virologic breakthrough at any time prior to this visit.

Cumulative treatment-emergent resistance:

Treatment-emergent resistance is defined as 1 log above nadir virologic breakthrough or HBV DNA >300 copies/mL confirmed by genotypic mutation. Cumulative treatment-emergent resistance at timepoint is defined as resistance at any time before or at the timepoint.

HBeAg loss/E-Loss:

HBeAg loss is defined as loss of detectable serum HBeAg in a patient who was HBeAg-positive at baseline. This endpoint is not defined for patients who were HBeAg-negative at baseline.

HBeAg seroconversion/E-seroconversion:

HBeAg seroconversion is defined as HBeAg loss and a gain of detectable HBeAb.

HBsAg loss/S-Loss:

HBsAg loss is defined as loss of detectable serum HBsAg in a patient who was HBsAg-positive at baseline. Since positive HBsAg is one of the study's inclusion criteria, this endpoint is defined for all randomized patients.

HBsAg seroconversion/S-seroconversion:

HBsAg seroconversion is defined as HBsAg loss and a gain of detectable HBsAb.

HBV DNA Change from baseline

HBV DNA change from baseline will be defined as the difference between the Week 24 HBV DNA value (log_{10} copies/mL) and baseline HBV DNA value (log_{10} copies/mL).

Time to achieve HBV DNA < 300 copies/mL

This endpoint will be defined in two ways: in the initial double-blind period and for the overall LdT treatment.

In the initial double-blind period time to achieve HBV DNA < 300 copies/mL is defined as the number of days from the baseline to the first on-treatment visit when the patient has achieved HBV DNA < 300 copies/mL. If the patient never achieves HBV DNA < 300 copies/mL while on the initial treatment (Placebo or LdT) and before his/her efficacy censoring date, the time is censored at the date of the last dose of the initial treatment or the efficacy censoring date, whichever comes first.

For the overall LdT treatment time to achieve HBV DNA < 300 copies/mL is defined for all subjects who were treated with LdT, including those initially randomized to LdT and those initially randomized to placebo, but switching to LdT after Week 24. Subjects who were never treated with LdT will be excluded, as well as subjects, if any, who achieved HBV DNA < 300 copies/mL during initial placebo treatment. Time to event will be calculated as the number of days from the first LdT dose to the first on-treatment visit when the patient has achieved HBV

DNA < 300 copies/mL. If the patient never achieves HBV DNA < 300 copies/mL before his/her efficacy censoring date, the time is censored at the efficacy censoring date.

Time to Initial Virologic Breakthrough

This endpoint will also be defined in two ways: in the initial double-blind period and for the overall LdT treatment.

In the initial double-blind period, for patients that experience Virologic Breakthrough while on initial treatment, time to Initial Virologic Breakthrough is defined as the number of days from the baseline to the first of the two visits when patient's HBV DNA is 1 log above nadir, as required by the Virologic Breakthrough definition. For patients that do not experience Virologic Breakthrough while on the initial treatment (Placebo or LdT) and before their efficacy censoring date, the time is censored at the date of the last dose of the initial treatment or the efficacy censoring date, whichever comes first.

For the overall LdT treatment time to Virologic Breakthrough is defined for all subjects who were treated with LdT, including those initially randomized to LdT and those initially randomized to placebo, but switching to LdT after Week 24. Subjects who were never treated with LdT will be excluded, as well as subjects who experienced Virologic Breakthrough during the initial placebo treatment. Time to event will be calculated as the number of days from the first LdT dose to the first of the two visits when patient's HBV DNA is 1 log above nadir, as required by the Virologic Breakthrough definition. If the patient never experiences Virologic Breaktrhough before his/her efficacy censoring date, the time is censored at the efficacy censoring date.

Primary non-response

A patient is defined to have primary non-response if after 12 weeks of treatment he/she has HBV DNA decline < 1log10 copies/mL from baseline for two consecutive visits.

Composite response

Composite response is defined as HBV DNA <300 copies/mL, ALT normalization (if patient had abnormal ALT at baseline) or normal ALT (if patient had normal ALT at baseline) and HBeAg seroconversion (if patient was HBeAg-positive at baseline) at the same visit. For patients who were HBeAg-negative at baseline the requirement of HBeAg seroconversion does not apply.

[redacted]

2.7.4 Analysis methods

2.7.4.1 Primary efficacy endpoint

The primary objective of this study is to evaluate the antiviral efficacy of telbivudine using the percentage of pediatric patients achieving HBV DNA <300 copies/mL (51 IU/mL) at Week 24. To this end, the proportion of patients achieving the primary efficacy endpoint will be presented for each treatment group for the FAS population. The proportions will be compared using Fisher's exact test with significance level of 5%. Two sided 95% exact confidence interval will be provided for the difference of proportions of the two groups.

[redacted]

To check the robustness of the primary analysis, two sets of supportive analyses will be performed:

1. Analysis on Per Protocol set.
2. Age group by baseline HBV DNA strata (low vs. high) adjusted estimate, using Mantel-Haenszel weighted estimated method, as described in Agresti and Hartzel (Agresti and Hartzel 2000). The younger age group will be pooled in to the middle age group, as there will be only a few patients in the younger age group. The details of the Mantel-Haenszel weighted estimated method are given in Appendix 1.

Secondary [redacted] efficacy endpoints

Secondary [redacted] efficacy endpoints can be grouped into three categories and all endpoints belong to a same category will be analyzed using the same approach. All endpoints will be analyzed for FAS and PPS.

2.7.4.2 Continuous endpoints

Continuous endpoints include serum HBV DNA in $\log_{10}$ copies/mL, serum ALT, [redacted]. Summary statistics of absolute value and of change from baseline, including means, standard deviations, medians, minimum and maximum will be presented by visit and treatment group.

These endpoints will be analyzed and compared between the treatment group using Analysis of Covariance (ANCOVA) model, including treatment, age group (<12 years vs. >= 12 years), baseline HBV DNA group (low or high), geographic region as classification effects and baseline value as covariate. Least Square means (LSMeans) for each treatment group will be

presented with their standard errors, as well as difference between LS means with its 95% confidence interval and p-value for the test of no treatment effect.

2.7.4.3 Dichotomous endpoints

Dichotomous endpoints include HBV DNA < 300 copies/mL, 1000 copies/mL and 10000copies/mL, HBV DNA < LLOQ, ALT normalization, HBeAg loss, HBeAg seroconversion, HBsAg loss, composite response, cumulative virologic breakthrough, cumulative treatment emergent genotypic resistance and primary non-response.

For dichotomous endpoints, statistical summaries will include counts and percentages of patients with a positive response (response rate), 95% confidence intervals for the difference in percentage between the treatment groups and p-value from the Fisher's exact test comparing the two treatment groups.

2.7.4.4 Time to event endpoints

Time to event endpoints include time to HBV DNA < 300 copies/mL, time to initial virologic breakthrough.

Estimates of median time to event with 95% confidence intervals will be provided by treatment group. The two groups will be compared using log-rank test.

[redacted]

2.8 Safety evaluation

All safety analyses will be performed on the safety set.

Safety information will be summarized for the on-treatment period, as defined in Section 2.1.4.

2.8.1 Adverse events

Adverse events will be coded by primary system organ class and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA) version 19.1.

Adverse events occurring in patients in the Initial Placebo group will be assigned to either Placebo or LdT treatment based on their onset date:

- Placebo: AEs with onset before the first date of LdT treatment after switching; for patients who did not switch to LdT, all AEs will be assigned to Placebo
- LdT: AEs with onset date on or after the first date of LdT treatment after switching.

The following treatment groups will be used for AE summaries:

- Initial LdT;
- Initial Placebo on Placebo treatment;

- Initial Placebo on LdT treatment after switching. The denominator for percentages in this group will be the total number of patients who switched from Placebo to LdT;
- All LdT (Initial LdT and Initial Placebo on LdT treatment after switching combined);
- Overall (all events combined).

The frequency and percentage of patients with adverse events will be summarized by treatment group. Levels of classification will include primary system organ class and preferred term and also by preferred term only. At each level of classification, a patient will be counted only once for each AE experienced within that level.

Adverse events will be deemed on-treatment if the onset date is on or after the date of first study drug administration and up to 30 days after the patient has stopped study treatment.

The following subgroups of adverse events will be summarized:

- Adverse events regardless of study drug relationship
- Adverse events suspected to be related to study drug
- Serious adverse events regardless of study drug relationship
- Serious adverse events suspected to be related to study drug
- Adverse events for patients who discontinued study due to an adverse event.
- Adverse events of special interest identified by the investigator
- Adverse events of special interest defined for LdT project.

In addition, patient listing will be provided for adverse events, serious adverse events and adverse events of special interest.

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on treatment-emergent adverse events that are not serious adverse events with an incidence greater than 5% and on treatment-emergent serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

Adverse events of special interest

The preferred terms to be used to identify adverse events of special interest for LdT project are provided in Appendix 2.

Death

Patient deaths, if any, will be listed.

2.8.2 Laboratory assessments

Descriptive statistics of the mean, median, standard deviation, minimum, maximum, and number of patients will be presented for the key laboratory parameters: ALT, AST, CK, serum creatinine, Cystatin C, Phosphate, Blood Glucose, Total Bilirubin, Albumin at all scheduled visits. This data will also be presented in listings.

2.8.3 Graded laboratory abnormalities

The frequency and percent of patients experiencing new on-set on-treatment grades 1/2 and 3/4 lab abnormality will be summarized by periods: baseline to Week 24, Week 24 to Week 52 , Week 52 to Week 104 and baseline to Week 104. For each parameter each patient will be assigned to the worst grade during the period.

2.8.4 ALT flares

ALT flares as defined by 2007 AASLD guideline (ALT elevation > 2× Baseline and ALT elevation > 10× ULN) will be summarized.

Proportion of patients experiencing on-treatment ALT flares will be summarized by periods: baseline to Week 24, Week 24 to Week 52, and baseline to week 52

In addition, data listings for patients who had on-treatment ALT flare will be presented.

2.8.5 Vital signs

Vital signs will include height, weight, systolic/diastolic pressure, heart rate, body temperature and respiration rate. Vital signs and their change from baseline will be summarized descriptively by scheduled visit.

2.8.6 Muscle symptoms

Patients with complaints of muscle weakness, muscle pain or achiness, or effort-related fatigue (summarized as muscle related events) will be administered Muscle Symptom Questionnaire and perform neuromuscular exam with strength testing. Results of the Muscle Symptom Questionnaire and neuromuscular exam with strength testing will be listed.

2.8.7 Glomerular filtration rate

Analysis of estimated Glomerular filtration rate (eGFR) will be performed by visit. GFR will be calculated by the Schwartz formula:

eGFR = 0.413×(height/serum creatinine) (height in cm; serum creatinine in mg/dL)

The height will be used as assessed at the closest visit.

Only on-treatment GFR values will be analyzed. Generally, analysis will be performed in two ways:

- "as observed", with no imputation of missing values

- with LOCF imputations of missing on-treatment values up to Week 24.

Simple summaries without statistical comparisons will be performed "as observed" only.

Mean, median, standard deviation, minimum and maximum values will be presented by visit. Actual GFR values as well as absolute and percent changes from baseline will be summarized. For each post-baseline visit, GFR values will be compared to baseline values within treatment groups with paired t-test. This summary will be created for the overall safety set as well as for two sub-populations of patients with renal function impairment at baseline:

1. eGFR < 60 mL/min/1.73m^2
2. 60-90 mL/min/1.73m^2
3. 60-80 mL/min/1.73m^2
4. > 90 mL/min/1.73m^2.

This summary will be performed both "as observed" with no imputations and with LOCF imputations.

Number and percentage of patients with abnormal baseline eGFR (60-90 mL/min/1.73m^2 or 60-80 mL/min/1.73m^2) shifting to normal eGFR (>90 mL/min/1.73m^2) at Week 24, 52 and 104 will be presented by treatment group. The shifting rate will be compared between the two treatment groups using Fisher's exact test. This summary will be performed both "as observed" with no imputations and with LOCF imputations.

Also, GFR will be categorized into the following categories: < 60, 60 – 90, >90. Shift table comparing GFR categories at each post-baseline visit to baseline will be created.

Percent change from baseline in GFR by MDRD formula over time will be presented graphically.

2.8.8 Relationship of muscle events and CK elevations

Muscle events (ME) are defined as adverse events with the preferred terms identified in "Appendix 2. Preferred terms for the Adverse Events of Special Interest" for the "Rhabdomyolysis/myopathy" category.

Only on-treatment MEs will be considered.

Abnormal CK value is defined as CK measurement higher than the upper limit of norm (ULN). *New-onset abnormal CK value* is defined as abnormal CK value with the grade higher than baseline CK grade.

A grade 3/4 abnormal CK episode is defined as a sequence of consecutive on-treatment visits with abnormal CK assessments of grade 3 or 4. The start of the episode is the first visit within the sequence with grade 3 or 4 CK, and the end of the episode is the last visit within the sequence with grade 3 or 4 CK.

A *new onset grade 3/4 abnormal CK episode* is defined as a grade 3/4 abnormal CK episode with the grade at the first visit higher than baseline CK grade. Only new onset grade 3/4 abnormal CK episodes will be considered.

The *resolution* of grade 3/4 abnormal CK episode is defined as follows:

- The episode is said to *resolve to normal* if there exists a normal CK assessment after the end of the episode and before the start of next episode or the patient's last on-treatment visit (whichever comes first).
- The episode is said to *resolve to grade 1/2* if it does not resolve to normal, however, there exists a CK assessment of grade 1 or 2 after the end of the episode and before the start of next episode or the patient's last on-treatment visit (whichever comes first).
- The episode is said to be *not resolved* if none of the above happened, i.e. grade 3 or 4 abnormal CK continued to the last on-treatment visit.

An episode is said to *return to baseline grade* if there exists a CK assessment with grade less than or equal to the baseline CK grade after the end of the episode and before the start of next episode or the patient's last on-treatment visit (whichever comes first).

An episode is said to resolve at last visit if at the patient's last on-treatment visit the CK value is normal or grade 1 or 2.

The following summaries describing muscle events, CK elevations and their relationship will be presented:

1. Proportion of patients with MEs, and among them:
    a. Experiencing any, grade 1/2, grade 3/4 new-onset abnormal CK during the study
    b. Experiencing any, grade 1/2, grade 3/4 new-onset abnormal CK within 30 days of the ME (i.e. in the period from ME start day minus 30 days to ME end day plus 30 days)
    c. Experiencing any, grade 1/2, grade 3/4 new-onset abnormal CK at the assessment closest to ME start.

    Only on-treatment CK assessments will be considered for this analysis.
2. Proportion of patients experiencing new-onset grade 3 or 4 abnormal CK episodes, and among them, experiencing and not experiencing ME in the study. Among those that do experience an ME within the study, proportion of patients with the ME within 30 days of the episode (i.e. in the period from start of episode minus 30 days to end of episode plus 30 days) and outside of 30 days of the episode. Only on-treatment CK assessments will be considered for this analysis.
3. Descriptive summary of CK levels and change from baseline at the study's scheduled visits and proportion of normal, abnormal, and grade 3/4 CK values at each visit. Only baseline and on-treatment CK values will be considered. Only patients with both

baseline and post baseline timepoint value (i.e. having a non-missing change from baseline) will be summarized at each timepoint.

4. Proportion of new onset grade 3/4 CK episodes by resolution.
5. To represent the relationship among baseline CK, on-treatment CK and MEs, the following proportions:
    a. Patients with abnormal baseline CK, and among them experiencing and not experiencing at least one on-treatment ME.
    b. Patients experiencing at least one on-treatment ME and among them with normal or abnormal (elevated) baseline CK.
    c. Patients with on-treatment new-onset abnormal CK of grade 3 or 4, and among them with having and not having abnormal CK at both baseline and screening visits.
6. For patients that experience at least one ME, descriptive summary of CK, ALT and AST levels at the visit closest to the first ME start and at the two visits preceding and two visits following the ME start.
7. For patients that experience at least one ME, breakdown of patients by ME preferred term (Myopathy, (Poly) myositis, Myalgia or Other MEs) and by the following CK assessments:
    a. Baseline CK (normal, grade 1 or 2, grade 3 or 4)
    b. CK level at closest assessment to ME start (normal, grade 1 or 2, grade 3 or 4)
    c. Highest on-treatment CK level during the study (normal, grade 1 or 2, grade 3 or 4)

In addition a listing of patients experiencing grade 3/4 abnormal CK within 30 days of ME will be provided, this will include all MEs and all CK assessments of these patients.

A graphical summary of median CK levels will be presented by visit. To maintain consistency with the table mentioned in item 3 above, only patients with both baseline and post baseline timepoint value (i.e. having a non-missing change from baseline) will be summarized at each timepoint.

All the above analyses will be performed on safety set.

2.8.9 Abdominal Ultrasound

Abdominal B-ultrasound will be performed at screening, Weeks 24, 52, 76, 104/End of treatment and 116/End of study. The investigator will record in the CRF if signs compatible with the context of chronic hepatitis B were observed and if signs of liver decompensation or HCC were observed. The frequency of responses will be summarized by treatment group and visit up to Week 24.

2.8.10 Tanner staging assessment

Assessment of sexual maturation in male and female patients (for age group >6 years at baseline visit) using Tanner staging will be performed at the following study visit: Baseline (visit 2), Week 24, Week 52 and Week 104. A frequency table of responses will be presented by treatment group and visit up to Week 24. All results will be listed.

2.9 Interim analyses

There is no interim analysis planned for this study. The primary analysis was planned at week 24 -when all patients complete 24 weeks of treatment. Additional analysis was planned to be conducted when all patients complete 52 weeks of treatment. Final analysis as planned to be conducted after all patients completed week 104 of the study. However, due to early termination of the study only one analysis will be performed summarizing all available data with focus on data up to Week 24.

2.10 Other topics

No other topics were studied.

3 Sample size and power considerations

The primary objective of this study is to demonstrate the antiviral efficacy with percentage of patients with attainment of HBV DNA < 300 copies/mL (51 IU/mL) in telbivudine treatment compared to placebo at Week 24 in patients with chronic hepatitis B.

Based on the results from CLDT600A2414 epidemiological study, 84-88% of pediatric patients presented HBV DNA < 9 $\log_{10}$ for HBeAg positive patients. In this study, 80% of patients with baseline HBV DNA < 9 $\log_{10}$ are expected to be recruited. Based on these baseline patients characteristics, the efficacy rate in the overall population is estimated to be 60%.

Considering a 5% dropout rate (and imputed values as failure (worst case)), with the assumptions of 60% and 5% patients with HBV DNA <300 copies/mL (51 IU/mL) at Week 24 for telbivudine and placebo arms, respectively a total of 150 patients with a randomization ratio of 5:1 for telbivudine: placebo (125 vs. 25) was expected to provide > 99% power to test the primary hypothesis, at 5% significance level, for overall patients population. However, due to early termination of the study the planned sample size was not achieved. Analysis will be performed on data available at the time of study termination.

4 Appendix 1. Mantel-Haenszel weighted estimated method

The method, as described in Agresti and Hartzel (2000), is as follows. The patients will be stratified by HBV DNA level (low, defined as < 9 log for HBeAg-positive patients and < 7 log for HBeAg negative vs. high, defined as >= 9 log for HbeAg-positive patients and >= 7 log for HBeAg negative) and age group (<12 years vs. >= 12 years) at baseline into 4 strata. Let's introduce the following notation:

n_{11k} is the number of patients in Strata K, Treatment group LdT, with a positive response.

n_{12k} is the number of patients in Strata K, Treatment group LdT, with a negative response.

n_{1+k} is the number of patients in Strata K, Treatment group LdT.

n_{21k} is the number of patients in Strata K, Treatment group Placebo with a positive response.

n_{22k} is the number of patients in Strata K, Treatment group Placebo, with a negative response.

n_{2+k} is the number of patients in Strata K, Treatment group Placebo.

n_{+1k} is the number of patients in Strata K with a positive response.

n_{+2k} is the number of patients in Strata K with a negative response.

n_{++k} is the number of patients in Strata K.

The Mantel-Haenszel proportion estimate controlling for strata is given by:

Telbivudine:

$$P_{LdT} = \frac{\sum_k w_k (n_{11k}/n_{1+k})}{\sum_k w_k}$$

Placebo:

$$P_{Placebo} = \frac{\sum_k w_k (n_{21k}/n_{2+k})}{\sum_k w_k}$$

Where

$$w_k = \frac{n_{1+k} \times n_{2+k}}{n_{++k}}$$

are the weights

The difference in proportion is given by $\Delta = P_{LdT} - P_{Placebo.}$

The variance estimate for the difference in proportions, Δ, is given by:

$$\mathrm{Var}(\Delta) = \frac{\Delta \times (\sum_k L_k) + (\sum_k M_k)}{(\sum_k w_k)^2}$$

where

$$L_k = (n_{1+k}^2 \times n_{21k} - n_{2+k}^2 \times n_{11k} + n_{1+k} \times n_{2+k}(n_{2+k} - n_{1+k})/2)/n_{++k}^2$$

and

$$M_k = (n_{11k} \times n_{22k} + n_{21k} \times n_{12k})/2n_{++k}$$

Two-sided confidence intervals for the difference in proportions will be of the form:
$\Delta \pm Z_{\alpha/2} \times sqrt(\mathrm{Var}(\Delta))$

Where $Z_{\alpha/2}$ is the 1–α/2 percentile from a standard normal distribution.

Two-sided p-value for the treatment group difference in proportions (versus 0) will be based on the estimated difference in proportions divided by the estimated standard error. Standard normal distribution theory for this statistic will be applied to estimate the p-value, such that it is consistent with the corresponding confidence interval, i.e.
$p = 1 - \Phi((\Delta + 0.1)/sqrt(\mathrm{Var}(\Delta))$

Where $\Phi(x)$ is the probability that an observation from the standard normal distribution is less than or equal to x.

5 Appendix 2. Preferred terms for the Adverse Events of Special Interest

Category	Preferred Terms
Blood creatine phosphokinase increased	Blood creatine phosphokinase abnormal Blood creatine phosphokinase increased Blood creatine phosphokinase MB abnormal Blood creatine phosphokinase MB increased Blood creatine phosphokinase MM increased
Rhabdomyolysis/myopathy	Muscle necrosis Myoglobin blood increased Myoglobin blood present Myoglobin urine present Myoglobinaemia Myoglobinuria Myopathy Myopathy toxic Necrotising myositis Rhabdomyolysis Acute kidney injury Anuria Biopsy muscle abnormal Blood calcium decreased Blood creatine phosphokinase abnormal Blood creatine phosphokinase increased Blood creatine phosphokinase MM increased Blood creatinine abnormal Blood creatinine increased Chromaturia

	Chronic kidney disease Compartment syndrome Creatinine renal clearance abnormal Creatinine renal clearance decreased Diaphragm muscle weakness Electromyogram abnormal End stage renal disease Glomerular filtration rate abnormal Glomerular filtration rate decreased Hypercreatininaemia Hypocalcaemia Muscle disorder Muscle enzyme increased Muscle fatigue Muscle haemorrhage Muscle rupture Muscular weakness Musculoskeletal discomfort Musculoskeletal disorder Musculoskeletal pain Myalgia Myalgia intercostal Myositis Oliguria Renal failure Renal impairment Renal tubular necrosis Tendon discomfort
Peripheral neuropathy	Acute painful neuropathy of rapid glycaemic control Acute polyneuropathy Amyotrophy Anti-myelin-associated glycoprotein associated polyneuropathy Autoimmune neuropathy Axonal neuropathy Biopsy peripheral nerve abnormal Decreased vibratory sense Demyelinating polyneuropathy Guillain-Barre syndrome

	Ischaemic neuropathy Loss of proprioception Miller Fisher syndrome Multifocal motor neuropathy Myelopathy Nerve conduction studies abnormal Neuralgia Neuritis Neuronal neuropathy Neuropathic muscular atrophy Neuropathy peripheral Notalgia paraesthetica Peripheral motor neuropathy Peripheral nervous system function test abnormal Peripheral sensorimotor neuropathy Peripheral sensory neuropathy Polyneuropathy Polyneuropathy chronic Polyneuropathy idiopathic progressive Radiation neuropathy Sensorimotor disorder Sensory disturbance Sensory loss Small fibre neuropathy Tick paralysis Toxic neuropathy Anti-ganglioside antibody positive Anti-myelin-associated glycoprotein antibodies positive Areflexia Autonomic failure syndrome Autonomic neuropathy Burning feet syndrome Burning sensation Decreased nasolabial fold Dysaesthesia Electromyogram abnormal Formication Gait disturbance

	Genital hypoaesthesia Hereditary motor and sensory neuropathy Hypoaesthesia Hyporeflexia Hypotonia Mononeuritis Mononeuropathy Mononeuropathy multiplex Motor dysfunction Muscle atrophy Muscular weakness Nerve degeneration Neuromuscular pain Neuromuscular toxicity Neuromyopathy Neuropathy vitamin B6 deficiency Neurotoxicity Paraesthesia Paraesthesia ear Peripheral nerve lesion Peripheral nerve palsy Peripheral nerve paresis Peroneal nerve palsy Phrenic nerve paralysis Skin burning sensation Temperature perception test decreased Tinel's sign Ulnar neuritis Vulvovaginal hypoaesthesia
ALT Flare in pt with chronic HBV treatment	Alanine aminotransferase abnormal Alanine aminotransferase increased
Lactic acidosis	Blood lactic acid increased Hyperlactacidaemia Lactic acidosis Acid base balance abnormal Acidosis Anion gap abnormal Anion gap increased Blood bicarbonate abnormal Blood bicarbonate decreased

	Blood gases abnormal Blood lactic acid abnormal Blood pH abnormal Blood pH decreased Coma acidotic Kussmaul respiration Metabolic acidosis PCO2 abnormal PCO2 decreased Urine lactic acid increased
Acute pancreatitis	Cullen's sign Grey Turner's sign Haemorrhagic necrotic pancreatitis Hereditary pancreatitis Ischaemic pancreatitis Oedematous pancreatitis Pancreatic abscess Pancreatic haemorrhage Pancreatic necrosis Pancreatic phlegmon Pancreatic pseudocyst Pancreatic pseudocyst drainage Pancreatitis Pancreatitis acute Pancreatitis haemorrhagic Pancreatitis necrotising Pancreatitis relapsing Pancreatorenal syndrome Pancreatic enzymes abnormal Pancreatic enzymes increased
Lack of efficacy (with/without antiviral resistance development)	Device defective Device failure Device ineffective Diet failure Drug effect decreased Drug effect delayed Drug effect incomplete Drug effect variable Drug half-life reduced Drug ineffective

	Drug ineffective for unapproved indication Drug level decreased Drug resistance Drug specific antibody present Drug tolerance Drug tolerance increased Multiple-drug resistance Paradoxical drug reaction Remission not achieved Tachyphylaxis Therapeutic product ineffective Therapeutic product ineffective for unapproved indication Therapeutic reaction time decreased Therapeutic response changed Therapeutic response decreased Therapeutic response delayed Therapeutic response shortened Therapy non-responder Therapy partial responder Treatment failure Vaccination failure Virologic failure Multiple-drug resistance Disease progression Condition aggravated Pathogen resistance
Hypersensitivity/allergy	Acute generalised exanthematous pustulosis Administration site dermatitis Administration site eczema Administration site hypersensitivity Administration site rash Administration site recall reaction Administration site urticaria Administration site vasculitis Allergic bronchitis Allergic colitis Allergic cough Allergic cystitis Allergic eosinophilia

	Allergic gastroenteritis Allergic hepatitis Allergic keratitis Allergic myocarditis Allergic oedema Allergic otitis externa Allergic otitis media Allergic pharyngitis Allergic respiratory disease Allergic respiratory symptom Allergic sinusitis Allergic transfusion reaction Allergy alert test positive Allergy test positive Allergy to immunoglobulin therapy Allergy to surgical sutures Allergy to vaccine Alveolitis allergic Anaphylactic reaction Anaphylactic shock Anaphylactic transfusion reaction Anaphylactoid reaction Anaphylactoid shock Anaphylaxis treatment Angioedema Antiallergic therapy Antiendomysial antibody positive Anti-neutrophil cytoplasmic antibody positive vasculitis Application site dermatitis Application site eczema Application site hypersensitivity Application site rash Application site recall reaction Application site urticaria Application site vasculitis Arthritis allergic Aspirin-exacerbated respiratory disease Atopy Blepharitis allergic

	Blood immunoglobulin E abnormal Blood immunoglobulin E increased Bromoderma Bronchospasm Catheter site dermatitis Catheter site eczema Catheter site hypersensitivity Catheter site rash Catheter site urticaria Catheter site vasculitis Chronic eosinophilic rhinosinusitis Chronic hyperplastic eosinophilic sinusitis Circulatory collapse Circumoral oedema Conjunctival oedema Conjunctivitis allergic Contact stomatitis Contrast media allergy Contrast media reaction Corneal oedema Cutaneous vasculitis Dennie-Morgan fold Dermatitis Dermatitis acneiform Dermatitis allergic Dermatitis atopic Dermatitis bullous Dermatitis contact Dermatitis exfoliative Dermatitis exfoliative generalised Dermatitis herpetiformis Dermatitis infected Dermatitis psoriasiform Device allergy Dialysis membrane reaction Distributive shock Documented hypersensitivity to administered product Drug cross-reactivity Drug eruption

	Drug hypersensitivity Drug provocation test Drug reaction with eosinophilia and systemic symptoms Eczema Eczema infantile Eczema nummular Eczema vaccinatum Eczema vesicular Eczema weeping Encephalitis allergic Encephalopathy allergic Eosinophilic granulomatosis with polyangiitis Epidermal necrosis Epidermolysis Epidermolysis bullosa Epiglottic oedema Erythema multiforme Erythema nodosum Exfoliative rash Eye allergy Eye oedema Eye swelling Eyelid oedema Face oedema Fixed drug eruption Giant papillary conjunctivitis Gingival oedema Gingival swelling Gleich's syndrome Haemorrhagic urticaria Hand dermatitis Henoch-Schonlein purpura Henoch-Schonlein purpura nephritis Heparin-induced thrombocytopenia Hereditary angioedema Hypersensitivity Hypersensitivity vasculitis Idiopathic urticaria Immediate post-injection reaction

	Immune thrombocytopenic purpura Immune tolerance induction Immune-mediated adverse reaction Implant site dermatitis Implant site hypersensitivity Implant site rash Implant site urticaria Incision site dermatitis Incision site rash Infusion site dermatitis Infusion site eczema Infusion site hypersensitivity Infusion site rash Infusion site recall reaction Infusion site urticaria Infusion site vasculitis Injection site dermatitis Injection site eczema Injection site hypersensitivity Injection site rash Injection site recall reaction Injection site urticaria Injection site vasculitis Instillation site hypersensitivity Instillation site rash Instillation site urticaria Interstitial granulomatous dermatitis Intestinal angioedema Iodine allergy Kaposi's varicelliform eruption Kounis syndrome Laryngeal oedema Laryngitis allergic Laryngospasm Laryngotracheal oedema Limbal swelling Lip oedema Lip swelling Mast cell degranulation present Medical device site dermatitis

	Medical device site eczema Medical device site hypersensitivity Medical device site rash Medical device site recall reaction Medical device site urticaria Mouth swelling Mucocutaneous rash Multiple allergies Nephritis allergic Nikolsky's sign Nodular rash Oculomucocutaneous syndrome Oculorespiratory syndrome Oedema mouth Oral allergy syndrome Oropharyngeal blistering Oropharyngeal spasm Oropharyngeal swelling Palatal oedema Palatal swelling Palisaded neutrophilic granulomatous dermatitis Palpable purpura Pathergy reaction Periorbital oedema Pharyngeal oedema Pruritus allergic Radioallergosorbent test positive Rash Rash erythematous Rash follicular Rash generalised Rash macular Rash maculo-papular Rash maculovesicular Rash morbilliform Rash neonatal Rash papulosquamous Rash pruritic Rash pustular

	Rash rubelliform Rash scarlatiniform Rash vesicular Reaction to azo-dyes Reaction to colouring Reaction to drug excipients Reaction to preservatives Red man syndrome Rhinitis allergic Scleral oedema Scleritis allergic Scrotal oedema Serum sickness Serum sickness-like reaction Shock Shock symptom Skin necrosis Skin reaction Skin test positive Solar urticaria Solvent sensitivity Stevens-Johnson syndrome Stoma site hypersensitivity Stoma site rash Swelling face Swollen tongue Symmetrical drug-related intertriginous and flexural exanthema Tongue oedema Toxic epidermal necrolysis Toxic skin eruption Tracheal oedema Type I hypersensitivity Type II hypersensitivity Type III immune complex mediated reaction Type IV hypersensitivity reaction Urticaria Urticaria cholinergic Urticaria chronic Urticaria contact

	Urticaria papular Urticaria physical Urticaria pigmentosa Urticaria vesiculosa Urticarial vasculitis Vaccination site dermatitis Vaccination site eczema Vaccination site exfoliation Vaccination site hypersensitivity Vaccination site rash Vaccination site recall reaction Vaccination site urticaria Vaccination site vasculitis Vaccination site vesicles Vaginal exfoliation Vaginal ulceration Vasculitic rash Vessel puncture site rash Vessel puncture site vesicles Vulval ulceration Vulvovaginal rash Vulvovaginal ulceration
Acute renal failure	Acute kidney injury Acute phosphate nephropathy Acute prerenal failure Anuria Azotaemia Continuous haemodiafiltration Dialysis Haemodialysis Haemofiltration Hyponatriuria Neonatal anuria Nephropathy toxic Oliguria Peritoneal dialysis Prerenal failure Renal failure Renal failure neonatal Renal impairment

	Renal impairment neonatal Albuminuria Blood creatinine abnormal Blood creatinine increased Blood urea abnormal Blood urea increased Blood urea nitrogen/creatinine ratio increased Creatinine renal clearance abnormal Creatinine renal clearance decreased Creatinine urine abnormal Creatinine urine decreased Crystal nephropathy Fractional excretion of sodium Glomerular filtration rate abnormal Glomerular filtration rate decreased Hypercreatininaemia Intradialytic parenteral nutrition Kidney injury molecule-1 Nephritis Oedema due to renal disease Protein urine present Proteinuria Renal function test abnormal Renal transplant Renal tubular disorder Renal tubular dysfunction Renal tubular necrosis Tubulointerstitial nephritis Urea renal clearance decreased Urine output decreased
Fertility Disorders	Adrenal androgen deficiency Adrenal androgen excess Adrenogenital syndrome Albright's disease Aspermia Asthenospermia Azoospermia Delayed puberty Dyspareunia Ejaculation delayed

	Ejaculation delayed Ejaculation disorder Ejaculation failure Erectile dysfunction Erection increased Female orgasmic disorder Female sexual arousal disorder Female sexual dysfunction Fertility increased Follicle stimulating hormone deficiency Genito-pelvic pain/penetration disorder Haematospermia HAIR-AN syndrome Hyperandrogenism Hypergonadism Hyperprogesteronism Hypogonadism Hypoprogesteronism Hypospermia Incomplete precocious puberty Infertility Infertility female Infertility male Libido decreased Libido disorder Libido increased Luteinising hormone deficiency Male orgasmic disorder Male sexual dysfunction Mauriac syndrome Necrospermia Nocturnal emission Oligospermia Organic erectile dysfunction Orgasm abnormal Orgasmic sensation decreased Painful ejaculation Painful erection Precocious puberty Premature ejaculation

	Priapism Primary ciliary dyskinesia Primary hypogonadism Pseudoprecocious puberty Psychogenic erectile dysfunction Pubertal failure Pyospermia Retrograde ejaculation Semen discolouration Sexual dysfunction Spermatogenesis abnormal Spermatorrhoea Spontaneous ejaculation Spontaneous penile erection Teratospermia Young's syndrome Antral follicle count Antral follicle count high Antral follicle count low Antral follicle count normal Fructose semen decreased Fructose semen increased Infertility tests Infertility tests abnormal Infertility tests normal pH semen pH semen abnormal pH semen decreased pH semen increased pH semen normal Prostatic fluid leukocytes increased Red blood cells semen Red blood cells semen negative Red blood cells semen positive Semen analysis Semen analysis abnormal Semen analysis normal Semen liquefaction Semen liquefaction abnormal Semen liquefaction normal

	Semen liquefaction prolonged Semen liquefaction shortened Semen viscosity Semen viscosity abnormal Semen viscosity decreased Semen viscosity increased Semen viscosity normal Semen volume abnormal Semen volume decreased Semen volume increased Semen volume normal Sperm analysis Sperm analysis abnormal Sperm analysis normal Sperm concentration Sperm concentration abnormal Sperm concentration decreased Sperm concentration increased Sperm concentration normal Sperm concentration zero Spermatozoa abnormal Spermatozoa morphology Spermatozoa morphology abnormal Spermatozoa morphology normal Spermatozoa progressive motility Spermatozoa progressive motility abnormal Spermatozoa progressive motility decreased Spermatozoa progressive motility normal Total sperm count Total sperm count decreased White blood cells semen White blood cells semen negative White blood cells semen positive

6 Appendix 3: Protocol Deviations

Deviation code	Text description	Identification Method	Identification Clarification
C01	Compliance was fair (70-89%) on > 2 consecutive visits	Direct Hit Programming	If compliance was fair on > 2 consecutive visits, it would be a PD counted from the first time it occurred
C02	Compliance is poor (<70%) >=1 visit at any time during the study.	Direct Hit Programming	If compliance is poor >=1 visit at any time during the study, it would be a PD, counted from the first time it occurred
C03	Patient receives expired study drug	Manual by FM	Information needs to be in patient files
C04A	Patient receives incorrect dosing	Direct Hit Programming	For Any age and weight < 30kg; total daily dose administered ranges <20 mg or >600 mg
C04B	Patient receives incorrect dosing	Direct Hit Programming	If weight ≥ 30kg; total daily dose administered ≠ 600 mg
D01	Withdrawal of informed consent and/ or Assent	Manual by FM	Study treatment has not been discontinued and parents or legal guardian has withdrawn consent
I01C	Patient does not sign adult informed consent, after turning 18 years old, while on trial	Manual by FM	Patient does not sign adult informed consent, after turning 18 years old, while on trial
I01D	Patient turning 13 and at next visit failed to sign ICF and Assent for 13-18 years of age.	Manual by FM	Patient turning 13 and at next visit failed to sign ICF and Assent for 13-18 years of age.
D02A	Patients ALT>10xULN and > 2× baseline but patient not discontinued from the study.	Manual by FM	Visit 3 visit date onwards
D02B	Patient has ALT>3xULN and> 2x baseline value AND (TBiL>2 x ULN or INR>1.5) and not discontinued from the study.	Manual by FM	Visit 3 visit date onwards

D02C	Patient has hepatic decompensation (Child-Pugh B or C) but patient not discontinued from the study.	Manual by FM	Visit 3 visit date onwards
D03	Study treatment has not been discontinued: Patient is diagnosed with cancer	Manual by FM	Patient is diagnosed with cancer (other than basal cell or squamous cell carcinoma) including but not limited to HCC – Visit 2 date onwards
D04	Patient met muscle algorithm criteria for discontinuation (strength, symptoms, abnormal lab data) but was not discontinued	Manual by FM	Patients experiencing muscle related symptoms as indicated in Section 7.7. Visit 2 date onwards
D05	Study treatment has not been discontinued: Patient co-infected with HCV, HDV or HIV	Manual by FM	Patient co-infected with HCV, HDV or HIV. Visit 2 date onwards.
D06	Study treatment has not been discontinued: Patient having an adverse event that affecting physical growth	Manual by FM	Study treatment has not been discontinued: Patient having an adverse event that affecting physical growth
D07	Study treatment has not been discontinued: while presenting laboratory abnormalities which could affect study treatment (e.g. eGFR < 50 mL/min)	Manual by FM	According to protocol, it should be based on investigator's opinion
D08	Study treatment has not been discontinued: Patient was pregnant while on study	Direct Hit Programming	Pregnancy was confirmed and patient was not discontinued
D09	Study treatment has not been discontinued at Week 28, while patient was confirmed HBV DNA >= 300 copies at Week 24, and was on LDT	Manual by FM	Study treatment has not been discontinued at Week 28, while patient was confirmed HBV DNA >= 300 copies at Week 24, and was on LDT
D10A	Patient on placebo until Week24, started with telbivudine even when found not meeting the eligibility criteria to receive telbivudine at Week28 or at a later visit until week 52	Direct Hit Programming	Patient on placebo until Week24, started with telbivudine even when found not meeting the eligibility criteria to receive telbivudine at Week28 or at a later visit until week 52

D10B	Patient on placebo until Week24, started with telbivudine even when found not meeting the eligibility criteria to receive telbivudine at Week28 or at a later visit until week 52	Direct Hit Programming	Patient on placebo until Week24, started with telbivudine even when found not meeting the eligibility criteria to receive telbivudine at Week28 or at a later visit until week 52
D11	Patients, while being treated with placebo until Week24, who started receiving telbivudine at Week 28, did not discontinued from the trial even after having HBV DNA >= 300 copies/ml at Week 52	Direct Hit Programming	Patients, while being treated with placebo until Week24, who started receiving telbivudine at Week 28, did not discontinued from the trial even after having HBV DNA >= 300 copies/ml at Week 52
D12	Patients, while being treated with placebo until Week24, who started receiving telbivudine at Week 40, did not discontinued from the trial even after having HBV DNA >= 300 copies/ml at Week 64	Direct Hit Programming	Patients, while being treated with placebo until Week24, who started receiving telbivudine at Week 40, did not discontinued from the trial even after having HBV DNA >= 300 copies/ml at Week 64
D13	Patients, while being treated with placebo until Week24, who started receiving telbivudine at Week 52, did not discontinued from the trial even after having HBV DNA>= 300 copies/ml at Week 76	Direct Hit Programming	Patients, while being treated with placebo until Week24, who started receiving telbivudine at Week 52, did not discontinued from the trial even after having HBV DNA>= 300 copies/ml at Week 76
D14	Study treatment has not been discontinued while unplanned unblinding of the treatment occurred	Manual by FM	Treatment unblinding unplanned and without emergency need as judged by the treating physician
D15	Study treatment has not been discontinued while patient presented a virological breakthrough or genotypic resistance after 24 weeks of LDT treatment	Direct Hit Programming	Study treatment has not been discontinued while patient presented a virological breakthrough or genotypic resistance after 24 weeks of LDT treatment

E01	Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half lives of enrollment whichever is longer	Manual by FM	Use of other investigational drugs Information needs to be in patient files
E02	History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes	Manual by FM	Patient has a history of hypersensitivity to any of the study drugs or to drugs of similar chemical classes. Information needs to be in patient files
E03A	Patient has history of malignancy of any organ system (other than localized basal cell carcinoma of the skin) within the past 5 years	Manual by FM	Patient has history of malignancy of any organ system Information needs to be in patient files
E03B	Patient has ultrasonographic findings of hepatic mass and/or elevated AFP suggestive of possible HCC and is enrolled in the study	Manual by FM	Patient with ultrasonographic findings of hepatic mass and/or elevated AFP suggestive of possible HCC, should have the disease ruled-out prior to entrance into the study
E04	Confirmed positive serum test or beta-HCG laboratory test (5 IU/L or mIU/mL) and patient not withdrawn	Direct Hit Programming	Patient is pregnant. Confirmed by a positive beta-HCG laboratory test (> 5 IU/L or mIU/mL)- Information needs to be in patient files
E05	Women of child-bearing potential not using effective contraception methods	Manual by FM	Effective contraception include: • Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception • Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository • Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception • Placement of an intrauterine device (IUD) or intrauterine system (IUS) In case of use of oral contraception female subjects should have been stable on the same pill for a minimum of 3 months before taking study treatment.

E06	Sexually active adolescent males not using a condom during intercourse while taking drug and for 12 days after stopping medication and father a child	Manual by FM	Sexually active adolescent males not using a condom during intercourse while taking drug and for 12 days after stopping medication and father a child
E07	Patients with acute or chronic infection of HCV, HDV, HIV, or with acute infection of HAV, HEV, CMV or EBV	Manual by FM	Patient is co-infected with acute or chronic HCV, HDV or HIV infection and with acute infection of HAV, HEV, CMV or EBV at V1 or Baseline.
E08	Patient has received treatment of interferon or any other immunomodulatory agents within the last 12 months prior to screening.	Manual by FM	Patient has received treatment of interferon or any other immunomodulatory agents within the last 12 months prior to screening.
E09	Patient was treated with nucleoside or nucleotide drugs or other anti-CHB treatment (approved or investigational) at any time before screening.	Manual by FM	Patients need to be treatment naive with nucleos(t)ides. Information needs to be in patient files
E10A	Patient has medical condition that requires frequent use of systemic corticosteroids.	Manual by FM	Patient use of systemic corticosteroids, (topical and inhaled corticosteroids are allowed). Information needs to be in patient files
E10B	Patient has medical condition that requires frequent use of systemic acyclovir or famcyclovir	Manual by FM	Patient use of systemic acyclovir or famcyclovir. Information needs to be in patient files
E11	Patient has decompensated liver disease defined as a Child-Turcotte-Pugh score of > =7 (B or C)	Manual by FM	Patient had clinical signs/symptoms of hepatic decompensation with Child-Pugh score of B or C Information needs to be in patient files
E12	Patient has-one or more additional known primary or secondary causes of liver disease	Manual by FM	Patient has one or more additional known primary or secondary causes of liver disease
E13	Patient is liver or other organ transplant recipient, or bone marrow transplant recipient	Manual by FM	Patient is organ or bone marrow transplant recipient Information needs to be in patient files
E14	Patient is currently abusing illicit drugs, or has a history of illicit substance abuse.	Manual by FM	Patient is currently abusing illicit drugs, or has a history of illicit substance abuse.

E15	Patient is not abstinent from alcohol during the course of the study	Manual by FM	Patient is not abstinent from alcohol during the course of the study
E16	Patient has a medical condition requiring the chronic or prolonged use of potentially hepatotoxic drugs or nephrotoxic drugs or chemotherapy	Manual by FM	Use of chemotherapy Information needs to be in patient files
E18A	Patient has history of myopathy, myositis, or persistent muscle weakness or persistent high serum CK levels (>=7 ULN)	Manual by FM	Patient has history of myopathy, myositis, or persistent muscle weakness or persistent high CK levels ((≥7 ULN). Information needs to be in patient files
E18B	Muscular disease or abnormal neuromuscular signs or CK values at screening suggestive of muscular disease, or age at which independent walking first achieved after 16 months of age	Manual by FM	Patient has any muscular disease including but not limited to congenital / metabolic etiology, or with abnormal neuromuscular signs at screening or any screening CK values suggestive of muscular disease, or age at which independent walking first achieved after 16 months of age (based on birthday). Information needs to be in patient files
E19	Patient has received any drugs potentially associated with myopathy within 3 months prior to screening	Manual by FM	Patient has received any drugs potentially associated with myopathy (e.g. chloroquine, hydroxychloroquine, HMGCoA redutase inhibitors, fibric acid derivatives, penicilamine, zidovudine, cyclosporine, erythromycin, niacin, azole antifungals, etc) within 3 months prior to screening. Information needs to be in patient files
E20	Patient has at baseline other laboratory abnormalities as listed under exclusion criterion 20 in the protocol	Manual by FM	Patient has at baseline other laboratory abnormalities as listed under exclusion criterion 20 in the protocol
I01B	Patient has not provided Assent prior to study start.	Manual by FM	Assent (if requested) was not provided before study start
I01A	Informed consent not provided prior to any study related procedures were done	Manual by FM	Main ICF and Assent (if requested) was not provided before study start
I02A	Subject is <2 years	Direct Hit Programming	Subject is <2 years

I02B	Subject is >= 12 years and site=South Korea	Manual by FM	Derived Age is more than or equal to12 at Visit 1 Missing Age is a PD
I02C	Subject is >= 18 years at time of screening	Direct Hit Programming	Derived Age is more than or equal to18 at Visit 1 Missing Age is a PD
I04A	Non-detectable or not available serum HBsAg at the screening and at least once in the last 6 months prior to V1	Manual by FM	1) HBsAg was not detected or not available at Visit 1 visit date and not detected in the last 6 months prior to V1 2) HBsAg was detected at Visit 1 visit date but not in the last 6 months prior to V1 3) HBsAg was not detected at Visit 1 but was detected in the last 6 months prior to V1
I4B1	Patient HBeAg positive and serum HBV DNA < 5 log10 copies/ml (20 000 IU/L) at screening	Direct Hit Programming	Patient HBeAg positive and serum HBV DNA < 5 log10 copies/ml (20 000 IU/L) at screening
I4B2	Patient HBeAg positive and serum HBV DNA < 5 log10 copies/ml (20 000 IU/L) at visit 2 (baseline)	Direct Hit Programming	Patient HBeAg positive and serum HBV DNA < 5 log10 copies/ml (20 000 IU/L) at visit 2 (baseline)
I04C	Patient HBeAg positive and did NOT have serum ALT > or = 1.5×ULN and < 10×ULN (pediatric ULN) two times in the last 6 months beforeV1 or once during screening period	Manual by FM	Patient HBeAg positive and did NOT have serum ALT > or = 1.5×ULN and < 10×ULN (pediatric ULN) two times in the last 6 months beforeV1 or once during screening period
I04D	Patient HBeAg negative and serum HBV DNA < 4 log10 copies/ml (2 000 IU/L) at screening	Direct Hit Programming	Patient HBeAg negative and serum HBV DNA < 4 log10 copies/ml (2 000 IU/L) at screening CHK should fire only for randomized subject
I4D1	Patient HBeAg negative and serum HBV DNA < 4 log10 copies/ml (2 000 IU/L) at baseline	Direct Hit Programming	Patient HBeAg negative and serum HBV DNA < 4 log10 copies/ml (2 000 IU/L) at baseline
I04E	Patient HBeAg negative and did not have ALT > or =1 xULN and <10×ULN (pediatric ULN) two times in the last 12 months before V1 or once during screening period	Manual by FM	Patient HBeAg negative and did not have ALT > or =1 xULN and <10×ULN (pediatric ULN) two times in the last 12 months before V1 or once during screening period

I4B3	ALT >= 10 ULN (pediatric) at screening or baseline pre-treatment visit	Manual by FM	ALT >= 10 ULN (pediatric) at screening or baseline pre-treatment visit
M01	Patient has taken prohibited treatment	Manual by FM	Patient took any drug which has any known or potential risks for pediatrics population in terms of growth, bone, liver, neurological system, etc.
M02	Patient has taken prohibited treatment and prohibited treatment not stopped Section 5.5.8, Table 5-2	Manual by FM	Patient took any of the following prohibited treatments: drugs with known potential risks for pediatric population in terms of growth bone, liver, neurological system, LAM, ADV, ETV, TDF, FTC, investigational drugs; systemic acyclovir or famciclovir, immune modulators such as IFN, thymosin, interleukins; systemic steroids; hepatoxic drugs such as dapsone, erythromycin, systemic azole anti-fungals, anti-tuberculosis drugs, toxic dose of acetaminophen/paracetamol, herbal medications; nephrotoxic drugs (aminoglycosides, amphotericin B, foscarnet, vancomycin, cyclosporine, tacrolimus, request use of NSAIDs or aspirin; alcohol or illicit drug abuse, Chemotherapy drugs for malignant diseases or immune-suppressive therapy for transplantation; drugs associated with myopathy (chloroquine, hydroxychloroquine, HMGCoA reductase inhibitors, fibric acid derivatives, penicilamine, zidovudine, cyclosporine, erythromycin, niacin, azole antifungals, etc.)
O02	Last drug intake (Week 104 - Treatment Period) >=2 days before last visit V13 date>	Direct Hit Programming	PD only in case the patient is Completer.
S01	Patient enrolls in another clinical trial	Manual by FM	Patient enrolls in another clinical trial of an investigational agent while participating in this study.
S02	Study drug intake is not the same as randomized arm according to IVRS	Manual by FM	The given study drug via IVRS randomization does not match actual intake of study drug from Visit 2 visit date until Visit 7 visit date
S05	Randomized placebo patients who are qualified for LDT treatment did not start treatment at relevant qualifying visit	Manual by FM	Initiation of study treatment was delayed after the patient became eligible for telbivudine treatment.

7 References

[Agresti and Hartzel (2000)] Strategies for comparing treatments on a binary response with multi-centre data. Stat Med; 19:115-1139.