

Global Clinical Development - General Medicine

LDT600A/Telbivudine

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**

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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
B-US	B-Ultra Sound
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 ( $\beta$ -HCG)	$\beta$ -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

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PK	Pharmacokinetic
p.o.	oral
PPS	per protocol set
PPW	Premature patient withdrawal
PT	Prothrombin time
PTY	Patient treatment years
q.d.	queaque die (daily)
SAE	serious adverse event
SDD	Study drug discontinuation
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

## Glossary of terms

AESI	For the purpose of this study, adverse events of special interest (AESI) include defined muscle-related events and renal function related events ( <a href="#">Section 7.7</a> )
ALT normalization	Elevated baseline ALT level return to below ULN during treatment
ALT flare	ALT elevation $>10 \times$ ULN and $>2 \times$ Baseline (AASLD definition)
Assessment	A procedure used to generate data required by the study
Baseline visit	Day 1 of treatment for patient schedule of events from which all subsequent visits are determined
Compliance (adherence) of the patient at each visit	The degree to which a patient correctly follows the intake of study drug according to the given schedule in the protocol. Using the pill or liquid volume count and the compliance questionnaire used by the investigator, the investigator will record whether compliance is good ( $\geq 90\%$ ), fair (70 – 89%) or poor (< 70%).
Control drug	Drugs(s) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Copies/mL & IU/mL	1 IU/mL = 5.9 copies/mL 51 IU/mL = 300 copies/mL 29 IU/mL = 169 copies/mL
Early Discontinuation visit	Day of final clinical and laboratory evaluation during the Treatment phase if a patient has prematurely withdrawn from the study and includes all evaluations performed at Week 104 visit
eGFR	Estimated Glomerular Filtration Rate, evaluated with the abbreviated Schwartz formula (Schwartz 2009): Abbreviated Schwartz formula: $eGFR = 0.413 \times (height/serum creatinine)$ (height in cm; serum creatinine in mg/dL)
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Genotypic Resistance	On treatment drug related resistance mutation while not present at baseline in a compliant patient with confirmed virological breakthrough (VB), or with HBV DNA $\geq 300$ 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), and confirmed by genotypic sequencing.
HBV DNA reduction	Change of HBV DNA from Baseline
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product.”
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This includes any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally does not include other

	treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage
International normalized ratio	The INR is used to standardize the results of Prothrombin Time.
Medication number	A unique identifier on the label of each investigational/study drug package in studies that dispense medication using an IRT system
Subject Number	A number assigned to each patient who enrolls into the study
Part	A subdivision of a single protocol into major design components. These parts often are independent of each other and have different populations or objectives. For example, a single dose design, a multiple dose design that are combined into one protocol, or the same design with different patient populations in each part.
PCR	An acronym for Polymerase Chain Reaction. PCR is a technique which is used to amplify the number of copies of a specific region of DNA, in order to produce enough DNA to be adequately tested.
Period	A subdivision of a cross-over study
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all investigational/study treatment administration and all assessments (including follow-up)
Primary Non-Response (PNR)	Treatment compliant patient with 12 weeks of treatment who fails to achieve a HBV DNA decline $\geq 1\log_{10}$ copies/mL ( $1\log_{10}$ IU/mL) from baseline for two consecutive visits is defined as Primary Non-Response.
Prothrombin Time (PT)	The Prothrombin time is used to evaluate the extrinsic pathway of coagulation.
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study/investigational treatment was discontinued whichever is later
Study drug/ treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug (s), active drug run-ins or background therapy
Study/investigational treatment discontinuation	Point/time when patient permanently stops taking study/investigational treatment for any reason; may or may not also be the point/time of premature patient withdrawal
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points
Virological Breakthrough (VB)	An increase of HBV DNA $\geq 1\log_{10}$ copies/mL ( $1\log_{10}$ IU/mL) above nadir (nadir=lowest on treatment HBV DNA value prior to the VB evaluation time point) <i>or</i> HBV DNA $\geq 300$ copies/mL (51 IU/mL) after initial response with HBV DNA $< 300$ copies/mL (51 IU/mL) Virological breakthrough should be confirmed on two consecutive visits within 4 weeks interval or at last on-treatment visit in non-PNR patients

## Amendment 2

### Amendment rationale

The purpose of amendment 2 is to add clarifications on the role of Data Monitoring Committee (DMC) and add clarifying wording for the timing of interim analyses.

### Changes to the protocol

Protocol [Section 3.5](#), [Section 8.4](#), [Section 9.6](#) and [Section 9.7](#) are updated.

A copy of this amended protocol will be sent to the Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) and Health Authorities.

### Summary of previous amendments

#### Amendment 1

The main purpose of this amendment is to reflect a [REDACTED] request regarding one of the inclusion criteria of the protocol. The request was made because of availability of an approved medication for the treatment of compensated, chronic Hepatitis B infection in South Korea, which eliminates children 12 years of age or older from study participation in South Korea. In addition, a number of changes are introduced to clarify ambiguities in inclusion and exclusion criteria and support improved enrollment in the study. Finally, a small number of editorial changes are implemented in support of these protocol amendment changes and to clarify other ambiguities in current language.

Although recruitment has been limited to date, it has become apparent from the experience of the small number of sites that have begun to recruit patients that certain clarifications and minor modifications to the protocol can greatly improve recruitment efforts.

#### The purpose of this amendment is to:

1. Update inclusion criteria for children enrolled in the Republic of South Korea by specified age groups to align with the availability of alternative treatments for CHBV infection for the specified age groups. It is also clarified that age limits apply to the study subject's age at time of randomization.
2. Clarify serum ALT criteria for study inclusion - the current language of the protocol is ambiguous, as it could be misinterpreted to allow for serum ALT samples to be repeated during the screening period. Eliminate the inclusion criterion for patients with normal ALT levels to substantiate moderate to severe hepatic inflammation by histology report or FibroScan.
3. Eliminate acute infection with HSV as exclusion criteria. Clarification was also made in the language concerning condom use by sexually active adolescents, as previous wording was not stated in a negative "exclusionary" manner.
4. Eliminate duplication of list of viral causes of infectious hepatitis ([Exclusion Criteria 7](#) and [12](#)).
5. Permit the inclusion of results of abdominal B-US performed within the month prior to screening in lieu of the ultrasound to be performed at the screening visit.

6. Clarify the timing of planned statistical analyses for the protocol and absence of a planned interim analysis in [Sections 9.6 and 9.7](#) to align with [Section 3.5](#).
7. Support provision of post-study medication to benefit patients where continued treatment is medically indicated and feasible from regulatory perspective.
8. Clarify the management of patient discontinuation and premature patient withdrawal.
9. Remove the Serum ALT requirements for eligibility criteria for placebo treated patients to start telbivudine treatment at week 28 ([Section 5.2](#)).
10. Reduce the number of required storage samples for assessment [REDACTED] in patients with Virological Breakthrough and genetic sequencing.
11. Reduce the number of assays to rule out other viral infections with a potential to cause hepatitis in order to align the protocol with current diagnostic practices and to reduce required blood volume for diagnostic tests.
12. Extend screening period up to 10 weeks in cases of operational or administrative issues (e.g. blood samples not reaching central laboratory in good condition or lost specimens, that require replacement of samples, delay in obtaining results) in order to complete assessment of eligibility criteria.
13. Implement other minor editorial changes and updating the assessments and Table of Events in [Section 6](#) to reflect these changes.

**Protocol synopsis**

<b>Protocol number</b>	CLDT600A2306
<b>Title</b>	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
<b>Brief title</b>	Study of efficacy and safety, tolerability and pharmacokinetics of telbivudine in children and adolescents with compensated chronic hepatitis B virus infection
<b>Sponsor and Clinical Phase</b>	Novartis Phase 3
<b>Investigation type</b>	Drug
<b>Study type</b>	Interventional
<b>Purpose and rationale</b>	The purpose of the study is to assess the efficacy and safety of telbivudine at a dose of 20 mg/kg up to a maximum of 600 mg q.d. in compensated pediatric HBeAg-positive and negative CHB patients aged 2 to <18 years with the indication of antiviral CHB treatment. This study is part of the commitments of the pediatric development plan for telbivudine in Europe and US.
<b>Primary Objective</b>	The primary objective of this study is to demonstrate the antiviral efficacy of telbivudine compared to placebo in pediatric patients (2- < 18 years) by determining the percentage of patients achieving serum HBV DNA level of <300 copies/mL (51 IU/mL) at Week 24.
<b>Secondary Objectives</b>	The main secondary objectives are to assess <ul style="list-style-type: none"><li>the antiviral efficacy as evaluated by the proportion of patients achieving HBV DNA&lt; 300 copies/mL (51 IU/mL) at Week 52 and Week 104</li><li>the biochemical response at Week 24, 52 and 104 as evaluated by proportion of patients whose baseline ALTs were abnormal and subsequently normalized</li><li>the serological response at Week 24, 52 and 104 (Proportion of HBeAg positive patients at baseline who subsequently have HBeAg loss and HBeAg seroconversion and proportion of HBsAg positive patients at baseline who subsequently have HBsAg loss and HBsAg seroconversion)</li><li>the percentage of patients achieving composite endpoints at Week 52 and 104 (evaluated by HBV DNA &lt; 300 copies/mL (51 IU/mL), ALT normalization and HBeAg seroconversion)</li><li>the cumulative rate of virological breakthrough (VB) at Week 52 and 104</li><li>the presence of treatment emergent genotypic resistance associated with VB, 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)</li></ul>

	<ul style="list-style-type: none"> <li>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; development of liver decompensation and/or HCC</li> </ul>
<b>Study design</b>	<p>This protocol will enroll HBeAg positive and HBeAg negative patients into a randomized, double-blind and placebo-controlled study. A screening period of 6 weeks (which may be extended up to 10 weeks in case of operational or administrative issues) 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.</p> <p>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 &lt;9 log<sub>10</sub> and HBeAg negative patients with HBV DNA &lt;7 log<sub>10</sub> copies/mL) are expected to be recruited.</p> <p>Subsets of patients by age 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.</p> <p>At the baseline visit, eligible patients will be randomized in a double blind method to telbivudine or placebo in a ratio 5:1. The total double-blind placebo-controlled period will be 24 weeks.</p> <p>At Week 24 (visit 6), all patients will be unblinded and HBV DNA level will be assessed:</p> <ul style="list-style-type: none"> <li>For telbivudine treated patients: Patients with HBV DNA &lt;300 copies/mL (51 IU/mL) at Week 24 will remain on telbivudine treatment until Week 104; Patients with confirmed HBV DNA ≥300 copies/mL (51 IU/mL) at Week 24 will be discontinued from study drug at the next visit (Week 28).</li> <li>For patients on placebo, eligibility to start telbivudine treatment will be checked at Week 24 (positive serum HBsAg at baseline and Week 24, for HBeAg positive patients: serum HBV DNA level ≥ 5 log<sub>10</sub> copies/mL (or 20 000 IU/mL); for HBeAg negative patients: serum HBV DNA level ≥ 4log<sub>10</sub> copies/mL (or 2000 IU/mL) at Week 24 and patients will initiate treatment with telbivudine at Week 28. After 24 weeks on telbivudine treatment (at Week 52), HBV DNA level will be assessed. Patients with HBV DNA &lt;300 copies/mL (51 IU/mL) will remain on treatment until last on-treatment study visit (Week 104); patients taking telbivudine with confirmed HBV DNA ≥300 copies/mL (51 IU/mL) will be discontinued from study after Week 52. Placebo patients not eligible to start treatment at Week 28 may continue to be followed in the study until Week 52 and start telbivudine treatment at a later visit until Week 52.</li> </ul>
<b>Population</b>	The study population will be comprised of male or female patients between 2 and <18 years of age (at time of randomization), with HBeAg-positive and HBeAg-negative CHB and compensated liver disease. In the Republic of South Korea, children aged 2 years to < 12 years only (at the time of randomization) will be enrolled. It is planned to randomize at least 150 patients from multiple centers worldwide.
<b>Inclusion criteria</b>	Key inclusion criteria:

	<ul style="list-style-type: none"> <li>• Male or female outpatients between 2 and &lt; 18 years of age (at the time of randomization), except in the Republic of South Korea, where children aged 2 years to &lt; 12 years (at the time of randomization) only will be enrolled.</li> <li>• Clinical history compatible with compensated chronic hepatitis B</li> <li>• Documented compensated chronic hepatitis B defined by the following: <ul style="list-style-type: none"> <li>◦ Positive serum HBsAg at screening and at least one other documentation of HBsAg positive at least 6 months prior to screening</li> <li>◦ For HBeAg positive patients at screening, significant biologic and/or histologic signs of disease activity following EASL guidelines recommendations for CHB pediatric patients (<a href="#">Sokal et al 2013</a>) <ul style="list-style-type: none"> <li>▪ serum HBV DNA level <math>\geq 5 \log_{10}</math> copies/mL (or 20 000 IU/mL) (COBAS Taqman®) at screening as assessed by central laboratory and</li> <li>▪ serum ALT <math>\geq 1.5 \times</math>ULN and &lt; <math>10 \times</math>ULN (pediatric ULN) either once during the screening period or twice (2 times) within the 6 months prior to screening</li> </ul> </li> <li>◦ For HBeAg negative patients at screening, significant biologic and/or histologic signs of disease activity following EASL guidelines recommendations for CHB pediatric patients (<a href="#">Sokal et al 2013</a>) <ul style="list-style-type: none"> <li>▪ serum HBV DNA level <math>\geq 4 \log_{10}</math> copies/mL (or 2 000 IU/mL) (COBAS Taqman®) at screening as assessed by central laboratory and</li> <li>▪ serum ALT <math>\geq 1.0 \times</math>ULN and &lt; <math>10 \times</math>ULN (pediatric ULN) either once during the screening period or twice (2 times) within the 12 months prior to screening</li> </ul> </li> </ul> </li> </ul>
<b>Exclusion criteria</b>	<p>Key exclusion criteria:</p> <ul style="list-style-type: none"> <li>• Patients with acute or chronic infection of HCV, HDV, HIV, or with acute infection of HAV, HEV, CMV or EBV.</li> <li>• Patient has received treatment of interferon or any other immunomodulatory agents within the last 12 months prior to screening</li> <li>• Patient has received treatment of any nucleoside or nucleotide drugs or other anti-CHB treatment (approved or investigational) at any time before screening</li> <li>• Patient has a medical condition that requires frequent use of systemic acyclovir or famciclovir, systemic corticosteroids (topical and inhaled corticosteroids are allowed).</li> <li>• Patient has a decompensated liver disease defined as a Child-Turcotte-Pugh (CTP) Score <math>\geq 7</math> (Class B or C).</li> <li>• Patient has one or more additional known primary or secondary causes of liver disease, other than infectious agents, including alcoholic or non-alcoholic liver disease, fatty liver, hepatobiliary disease, Wilson disease and alpha-1 antitrypsin deficiency, Gilbert's syndrome, Dubin-Johnson syndrome etc.</li> <li>• Liver transplant recipients. Organ or bone marrow transplant recipients.</li> </ul>

	<ul style="list-style-type: none"> <li>• Patient is currently abusing illicit drugs, or has a history of illicit substance abuse.</li> <li>• All patients are required to be abstinent from alcohol during the course of the study otherwise excluded.</li> <li>• Patient has a medical condition requiring the chronic or prolonged use of potentially hepatotoxic drugs or nephrotoxic drugs or chemotherapy</li> <li>• History of any other acute or chronic medical condition (including congenital diseases, metabolic diseases, malignant diseases, neurological disorders, nephrotic diseases, pancreatitis, autoimmune disorders, diabetes, etc.) that in the opinion of the investigator would make the patient unsuitable for inclusion into the study.</li> <li>• Patient has a history of myopathy, myositis, persistent muscle weakness or persistent high serum CK levels (<math>\geq 7 \times \text{ULN}</math>), 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 time first achieved after 16 months of age (based on birthday).</li> <li>• Patient receiving any drugs potentially associated with myopathy (e.g., chloroquine, hydroxychloroquine, HMGCoA reductase inhibitors, fibric acid derivatives, penicilamine, zidovudine, cyclosporine, erythromycin, niacin, azole antifungals, etc) within 3 months prior to screening</li> <li>• Any other clinical significant disease, condition or abnormality, unrelated to their HBV infection at screening, as assessed by the investigator, including: <ul style="list-style-type: none"> <li>• Hemoglobin &lt; 11 g/dL (110g/L) for males or &lt; 10 g/dL (100g/L) for females</li> <li>• Total WBC &lt; 3,500/mm<sup>3</sup> (<math>3.5 \times 10^9/\text{L}</math>)</li> <li>• Absolute neutrophil count (ANC) &lt; 1,500/mm<sup>3</sup> (<math>1.5 \times 10^9/\text{L}</math>)</li> <li>• Platelet count &lt; 120,000/mm<sup>3</sup> (<math>120 \times 10^9/\text{L}</math>)</li> <li>• Prothrombin time prolonged by more than 3 seconds (based on ULN; of the reference value); or INR &gt; 1.5</li> <li>• Serum amylases or lipase <math>\geq 1.5 \times \text{ULN}</math></li> <li>• Serum albumin (&lt;3.5g/dL); (&lt;35g/L)</li> <li>• Total bilirubin (<math>\geq 2.0 \times \text{ULN}</math>)</li> <li>• estimated GFR &lt; 50 mL/min using Schwartz formula</li> <li>• Serum phosphate &lt; 1.5 mg/dL</li> </ul> </li> </ul>
<b>Investigational and reference therapy</b>	<p>Patients will be assigned to one of the two treatment arms in a ratio 5:1</p> <p><b>Arm 1: Telbivudine:</b></p> <ul style="list-style-type: none"> <li>• patients of any age and weight &lt; 30kg: telbivudine oral solution (20 mg/mL): 20 mg/kg up to 600 mg q.d. corresponding to weight (kg) x1mL, p.o. once daily</li> <li>• patients &lt; 12 years old and weight <math>\geq 30\text{kg}</math>: telbivudine oral solution (20mg/mL), 600 mg/day corresponding to 30 mL p.o. once daily</li> <li>• patients <math>\geq 12</math> years old and weight <math>\geq 30\text{kg}</math>: telbivudine film-coated tablet, 600 mg/day, corresponding to 1 tablet p.o. once daily</li> </ul> <p><b>Arm 2: Placebo:</b></p> <ul style="list-style-type: none"> <li>• patients of any age and weight &lt; 30kg: placebo oral solution</li> </ul>

	<p>corresponding to weight (kg) x1mL, p.o. once daily</p> <ul style="list-style-type: none"> <li>patients &lt; 12 years old and weight <math>\geq</math> 30kg: placebo oral solution corresponding to 30 mL p.o. once daily</li> <li>patients <math>\geq</math> 12 years old and weight <math>\geq</math> 30kg: placebo tablet, corresponding to 1 tablet p.o. once daily</li> </ul>
<b>Efficacy assessments</b>	<p>Key efficacy assessments include:</p> <ul style="list-style-type: none"> <li>Serum HBV DNA level</li> <li>HBV Serologic markers; HBsAg/Ab and HBeAg/Ab</li> <li>ALT</li> <li>VB and Resistance surveillance</li> </ul>
<b>Safety assessments</b>	<p>Key safety endpoints include:</p> <ul style="list-style-type: none"> <li>Proportion of patients that discontinue study drug or require dose interruption due to treatment-emergent AEs</li> <li>Proportion of patients who develop SAEs</li> <li>Proportion of patients who develop Grade 3-4 AEs and AEs related to study drug (and if study drug temporarily interrupted)</li> <li>Proportion of patients who develop AESI (muscle related events)</li> <li>Other classical adverse events related to anti-HBV nucleos(t)ides analogues (including peripheral neuropathy, ALT flare, lactic acidosis, acute pancreatitis and hypersensitivity reactions)</li> <li>Proportion of patients with hepatic decompensation or HCC</li> <li>Proportion of patients who develop Grade 3-4 chemistry abnormality (including CK, ALT, AST, ALP, TB, PT, serum creatinine, serum cystatin C, serum phosphate, blood glucose), urinalysis abnormality and Grade 3-4 hematology abnormalities</li> </ul> <p>Other safety assessments include physical exams (including growth (including Body weight, Body height and BMI) and development (Tanner Score), vital signs and pregnancy monitoring</p>
<b>Data analysis</b>	<p>The primary analysis will be performed when all patients complete Week 24. An additional analysis will be performed when all patients complete Week 52 and a report generated. Final analysis will be performed at the end of study including the 12 -week follow-up period after Week 104 treatment completion.</p> <p>The primary objective of the study is to demonstrate the antiviral efficacy of telbivudine compared to placebo in pediatric patients (2 - &lt; 18 years) by determining the percentage of patients achieving serum HBV DNA level of &lt;300 copies/mL (51 IU/mL) at Week 24. The Fisher Exact test method will be used to evaluate the null hypothesis (proportion of patients in the overall population achieving HBV DNA &lt;300 copies/mL (51 IU/mL) in the telbivudine arm is not different from in the placebo arm) and the alternative hypothesis (the proportion of patients in the overall population achieving HBV DNA &lt;300 copies/mL (51 IU/mL) between the two groups is not the same). Two sets of supportive analyses will be performed: (1) analysis on</p>

	<p>Per Protocol set and (2) Age by baseline HBV DNA strata (low vs. high) adjusted estimate, using Mantel-Haenszel weighted estimated method.</p> <p>The primary analysis will be done when all patients complete Week 24 of study and the final analysis will be done when all patients complete Week 104 of study.</p> <p>Secondary efficacy variables will be summarized by treatment groups; for Week 24 treatment comparison, dichotomous variables will be analyzed with Fisher's Exact Test, similar to primary efficacy analysis, and continuous variables will be analyzed with Analysis of Covariance (ANCOVA) model, including treatment, stratification factors, country/region and baseline values as co-factors. Time to event variables will be analyzed using survival analysis (Kaplan-Meier estimates).</p> <p>The safety analyses will be based on AEs, laboratory values, physical exams and vital signs. All safety data will be summarized by treatment group.</p>
<b>Key words</b>	Chronic hepatitis B, pediatrics, antiviral treatment, telbivudine

## 1 Introduction

### 1.1 Background

#### **Epidemiology and natural history of pediatric HBV infection**

More than 240 million people worldwide have chronic hepatitis B (CHB) infection ([WHO 2013](#)). The World Health Organization (WHO) and the World Gastroenterology Organization (WGO) recommend joint immune-prophylaxis with the hepatitis B vaccine (HBVAC) and HBIG to prevent mother-to-child transmission (MTCT) of HBV. Despite the introduction of universal infant vaccination since 1990, hepatitis B infection in children has not been eradicated ([Haber et al 2009](#)). Approximately 10% to 15% of neonates born to HBV infected mothers suffer from HBV infection through intrauterine transmission ([Farmer et al 1987](#); [Grosheide et al 1993](#)).

Children at risk for hepatitis B virus (HBV) infection include 1) those born to a mother who has CHB or 2) who are not vaccinated or not given immune globulin, or 3) had an inadequate response to perinatal treatment or vaccination, or 4) were exposed prior to being vaccinated ([Jonas et al 2010](#)).

The likelihood of chronic HBV infection in children is mainly determined by effectiveness of vaccination, the child's age at acquisition and by the transmission route. The likelihood of chronicity of HBV infection is almost 90% in patients infected by mother-to-child transmission; 25-50% in children between the ages of 1 to 5 years of age, and about 6 to 10% in older children ([Jonas et al 2010](#)). A Japanese survey has categorized the route of transmission of HBV to pediatric patients into five types of transmission: maternal, intra-familial horizontal, iatrogenic horizontal, other horizontal, and unknown ([Litsuka et al 2010](#)). Recently, a large, multi-center, cross-sectional study (LDT600A2414) designed to collect epidemiological data in 1640 patients with CHB aged 2 to <18 years showed that the majority of patients were Hepatitis B e-Antigen (HBeAg) positive, and older than 7 years ([Zhang et al 2012](#)).

Among adults who acquired CHB as an infant or child, ~ 15% to 25% overall die of premature liver-disease-related death ([Haber et al 2009](#)). Patients infected by HBV during childhood who have evidence of ongoing viral replication are at the highest risk for development of progressive liver disease ([Hsieh et al 1992](#)).

#### **Antiviral treatment goals and indication in pediatric CHB**

HBV infection in children presents a therapeutic challenge for the practitioner. Decisions regarding selection of patients who may benefit from treatment, appropriate timing of treatment, and the choice of antiviral therapy are complex and are confounded by the limited number of therapies that have been studied in children ([Jonas et al 2010](#)).

The current goals of antiviral therapy in children with CHB are to suppress viral replication, reduce liver inflammation, and reverse liver fibrosis, and thereby protect the liver. Treatment is geared toward reducing viral load until serum HBV DNA levels become undetectable by a sensitive polymerase chain reaction (PCR) assay and, for patients who are HBeAg-positive,

achieving durable HBeAg seroconversion. Another desirable endpoint is normalization of alanine aminotransferase (ALT) level, indicative of improvement in liver histology. Hepatitis B surface antigen (HBsAg) seroconversion occurs in a minority of persons receiving treatment, but it is the ultimate therapeutic goal because the risk of hepatocellular carcinoma (HCC) is reduced ([Jonas et al 2010](#)).

For children in the immune active or reactivation phases (mostly characterized by high HBV DNA and elevated ALT), liver histology can help guide treatment decisions, and family history of liver disease, especially hepatocellular carcinoma, may argue for early treatment in some cases. There are a few situations when treatment is indicated regardless of HBV DNA or alanine aminotransferase levels such as glomerulonephritis due to HBV infection, liver transplantation, immunosuppression or chemotherapy, etc. There is still much to be elucidated about the appropriate use of HBV therapy in children. Until more clinical data and therapeutic options are available, a conservative approach is warranted ([Jonas et al 2010](#)).

At this time, there is no established benefit of treatment for children in the immune tolerant phase which is characterized by high HBV DNA but persistent normal ALT levels ([Jonas et al 2010](#)). In addition, there is no indication for antiviral treatment of children in the “inactive HBsAg carrier” state which is characterized by undetectable or low HBV DNA and normal ALT levels ([Jonas et al 2010](#)).

### **Current treatment options**

There are now seven drugs worldwide approved for treatment of adult patients with CHB: two forms of interferon (i.e., common IFN alfa and peg interferon alfa (peg-IFN)), as well as five nucleos(t)ide analogues: lamivudine (LAM), adefovir dipivoxil (ADV), entecavir (ETV), telbivudine (LDT), and tenofovir disoproxil fumarate (TDF). None of these seven drugs is currently approved in Europe for the treatment of children suffering from CHB. LAM, ADV, TDF and common IFN-alfa are approved in the US for use in pediatric patients with CHB. In the US, lamivudine may be used from 2 to 17 years of age, adefovir and tenofovir for those aged 12 years and older, and common IFN-alfa for patients as young as 12 months of age. Treatment is not usually required for children under the age of 1 year.

In the randomized, open-label, placebo-controlled study of LAM, after 52 weeks of treatment 23% of children in the LAM group (n=191) vs. 13% in the placebo group (n=95) (p=0.04) achieved virologic response (i.e., undetectable HBV DNA and HBeAg loss). At Week 52, 61% patients in the LAM group vs. 16% in placebo group (p < 0.001) achieved undetectable HBV DNA rates (based on branched-chain DNA assay with a lower limit of detection of 0.7 meq / mL, approximately  $7 \times 10^5$  copies/mL) ([Jonas et al 2002](#)).

In the multicenter, randomized, double-blind, placebo-controlled ADV pivotal trial in pediatric CHB patients, at the end of 48 weeks 19.1% of the patients in the ADV group (n=115) vs. 1.7% in the placebo group (n=58) (p < 0.001) reached the primary endpoint of serum HBV DNA <1,000 copies/mL and normal ALT. At Week 48, 11% in the ADV group vs. 2% in placebo group (no p value in the reference) achieved HBV DNA undetectable rates (based on COBAS Taqman® assay with a lower limit of quantitation of 29 IU/mL, equivalent to 169 copies/mL) ([Jonas et al 2008](#)).

In the multicenter, randomized, double-blind, placebo-controlled phase III pivotal trial in adolescent CHB patients aged 12 to < 18 years; at Week 72, 89% of TDF treated patients (n=52) vs. 0% in placebo treated patients (n=54) achieved HBV DNA < 400 copies/mL ([Murray et al 2012](#)).

A phase 2b ETV pharmacokinetics and efficacy clinical trial in patients as young as 2 years old, as well as a phase 3 study are currently underway ([Jonas et al 2010](#)).

In the multinational, randomized, open-label, placebo-controlled trial of IFN-alfa therapy in pediatric CHB patients, 26% of IFN treated children (n=72) vs. 11% of untreated controls (n=77) (p=0.029) became HBeAg and HBV DNA negative at the end of 24 weeks of treatment. At Week 24, 22.9% in IFN vs. 6.5% in placebo group (no p value in the reference) achieved undetectable HBV DNA rates (based on liquid hybridization technique that detects viral genome at levels at or above 1.6pg/mL, approximately  $4 \times 10^5$  copies/mL) ([Sokal et al 1998](#)).

### **Epidemiological survey: CLDT600A2414**

The study CLDT600A2414 was a cross-sectional, epidemiological multi-center retrospective data collection survey in Western and Asian countries in pediatric patients with chronic HBV infection aged from 2 to <18 years. This survey was conducted to support the feasibility of conducting the phase III pediatric clinical development program for telbivudine, and to adequately design future studies part of Novartis telbivudine clinical pediatric program. The survey was initiated in June 2009 involving 80 centers and was closed in September 2011, after 1640 patients enrolled from 17 countries.

The main results were summarized as below:

#### **Demographic**

The mean age was 11.8 years. Most patients were aged 13 to < 18 years (52.6%), children aged 2-6 years represented 17.3% and children aged 7-12 year represented 30.1%.

#### **Disease Status**

The majority of patients were HBeAg-positive (54.4%) vs HBeAg negative (32.4%). For the 892 HBeAg positive, the HBV DNA level of the three measurements was < 9  $\log_{10}$  copies/mL in 84-88% of patients and for the 532 HBeAg negative patients, HBV DNA level was <7  $\log_{10}$  copies/mL in 87-93% of patients .

The disease was stable for the majority of patients (disease progression over the last 12 months was reported in 4.2% of the overall population). The ALT level was low for the majority of patients (ALT < 63-66 IU/L in 75% of HBeAg positive patients and ALT< 40-50 IU/L in 75% of HBeAg negative patients).

#### **Treatment status**

About 37.3% of patients previously received treatment or currently receiving treatment during the survey with a higher proportion in 13-<18 year age group (42.8%) as compared to 2-6 year age group (31.4%) and 7-12 year age group (31.2%) .

#### **New diagnosed or clinically managed CHB patients**

On 78 centers the mean number of patients aged from 2 to < 18 years newly diagnosed with HBV per year was 43 in 2008, 40 in 2007 and 38 in 2006. The mean number of clinically treated patients for HBV was 43 in 2008, 41 in 2007 and 40 in 2006.

## Summary

The results of the epidemiological study provide a comprehensive understanding of chronic HBV infection in the pediatric population worldwide and provide basic information on the feasibility for clinical trials in pediatric CHB patients.

Based on 1640 enrolled pediatric CHB patients from 80 clinical sites, this epidemiological survey reported the key patient's characteristics:

- The disease prevalence was higher for patient from age group 13 - <18 years (52.6%)
- The majority of patients were HBeAg positive with a majority of them having an HBV DNA  $<9 \log_{10}$  copies/mL (84-88%)
- The disease progression over last 12 months was stable for the majority (>80%) of patients in all countries assessed

## Telbivudine introduction

Telbivudine (Sebivo®/Tyzeka®) is approved for the treatment of CHB in adult patients with compensated liver disease and evidence of viral replication, persistently elevated serum ALT levels and histological evidence of active inflammation and/or fibrosis ([Telbivudine CDS](#)). Telbivudine ( $\beta$ -L-2'-deoxythymidine; LdT), is a deoxynucleoside with the L-configuration of thymidine and a highly specific and potent inhibitor of HBV replication in vitro ([Bryant et al 2001](#)). Robust data from preclinical and clinical studies in adults indicate that telbivudine provides effective antiviral activity with a favorable safety profile.

In the pivotal GLOBE trial, a phase III randomized, double-blind, active-controlled study to compare telbivudine versus LAM, telbivudine demonstrated statistically significant superiority over LAM in HBeAg-positive and HBeAg negative adults patients on most key study endpoints after 52 and 104 weeks, respectively ([Lai et al 2007](#); [Liaw et al 2009](#)).

There are 2 formulations of telbivudine, 600 mg film-coated tablets and 20 mg/mL oral solution. The recommended telbivudine dose in adult patients with chronic hepatitis B is 600 mg administered once daily.

A phase I pharmacokinetics study (CLDT600A2104) of Sebivo® 20mg/mL oral solution has explored the pharmacokinetics and safety of a single dose of telbivudine in pediatric CHB patients. Based on the data from this study in subjects aged 2 to <18 years a dose of 20mg/kg up to a maximum of 600 mg/day would give exposure to telbivudine in children similar to that which has been demonstrated to be safe and effective for the treatment of CHB in adults ([Section 3.3](#)).

Telbivudine is readily bioavailable following oral administration, is rapidly absorbed, and widely distributed throughout the body, and exhibits dose-proportional pharmacokinetics and dose/exposure-related anti-HBV activity. The oral solution and the tablet formulations are bioequivalent and approved for marketing in multiple countries.

More details about telbivudine are provided in the IB ([Sebivo IB](#)).

## 1.2 Purpose

The purpose of the study is to assess the efficacy and safety of telbivudine at a dose of 20 mg/kg up to a maximum of 600 mg q.d. in compensated pediatric HBeAg-positive and negative CHB patients aged from 2 to <18 years with the indication to antiviral CHB treatment. This study is part of the commitments of the pediatric development plan for telbivudine in Europe and US.

## 2 Study objectives

### 2.1 Primary and key secondary objectives

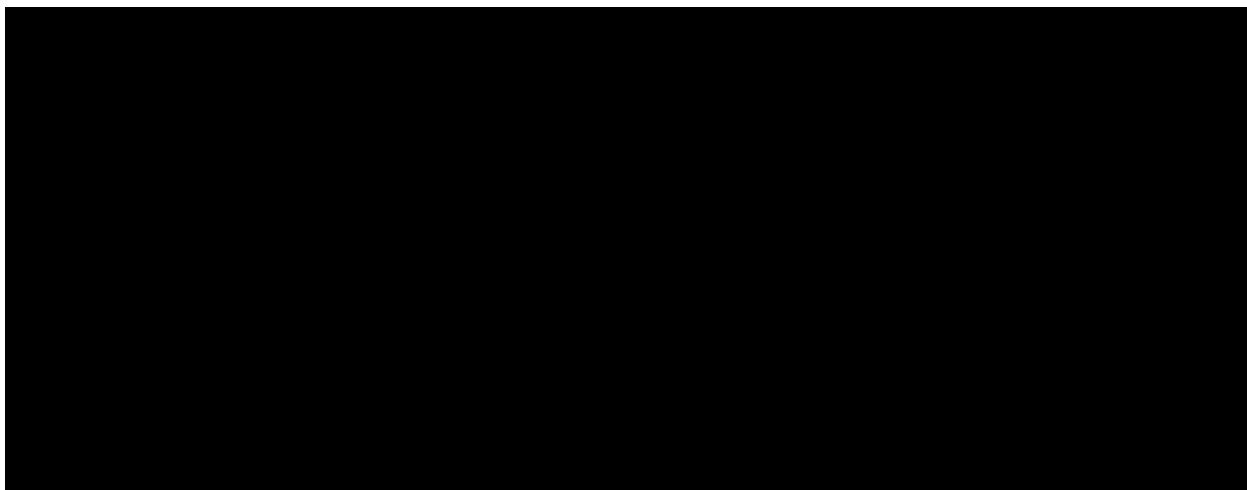
The primary objective of this study is to demonstrate the antiviral efficacy of telbivudine compared to placebo in pediatric patients by determining the percentage of patients achieving serum HBV DNA level of <300 copies/mL (51 IU/mL) at Week 24.

### 2.2 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,  $\geq$  LLOQ defined as detectable HBV DNA), <1000 copies/ml (or 200 IU/mL), <10,000 copies/ml (or 2 000 IU/mL) and  $\geq$ 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  $>1 \times$  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 $\geq$ 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



### **3      Investigational plan**

#### **3.1     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 6-10 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

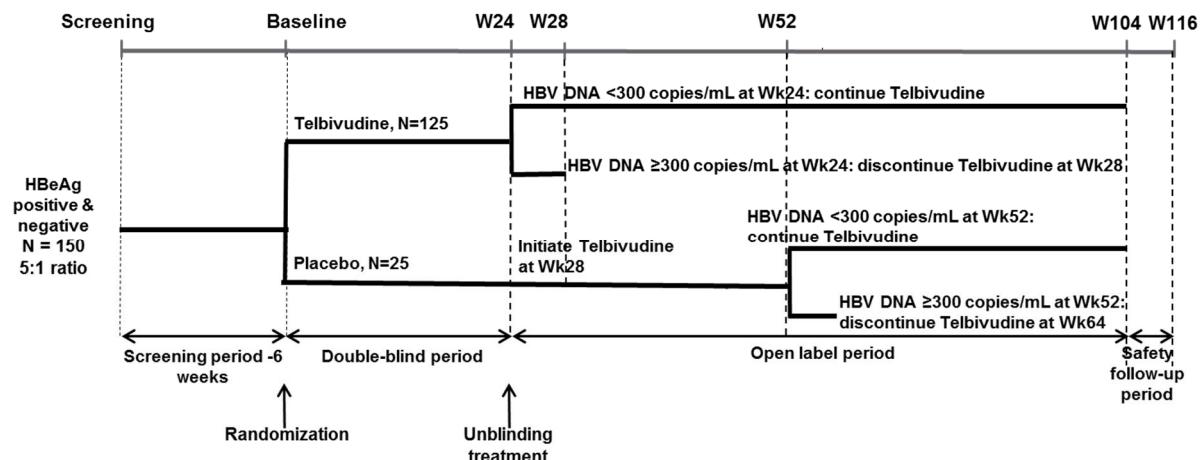


At Baseline (visit 2), eligible patients will be randomized in a double blind method to telbivudine or placebo in a ratio 5:1. The total double-blind period will be 24 weeks.

At Week 24 (visit 6), all patients will be unblinded (see [Section 5.4](#)):

- 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 receiving telbivudine treatment with confirmed HBV DNA  $\geq$ 300 copies/mL (51 IU/mL) at Week 24 (visit 6) will be discontinued from study drug at the next visit (Week 28) as described in [Section 5.5.9](#).
- 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  $\geq$ 300 copies/mL (51 IU/mL) will be discontinued from the study at Week 52 (visit 9) as described in [Section 5.5.9](#).
  - 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

**Figure 3-1** **Study design\***



\*Note: Screening period may be extended up to 10 weeks in case of operational or administrative issues.

### 3.2 Rationale of study design

This protocol will evaluate HBeAg positive and HBeAg negative patients with randomized, double-blind, and placebo-controlled design. A randomized double-blinded study design is well-established for the class of drug investigated. Patients and investigator will be blinded to treatment for 24 weeks and the primary efficacy endpoint will be assessed at Week 24.

Immunotolerant patients defined as HBeAg-positive, with high serum levels of HBV DNA and normal serum ALT are generally considered as not eligible for treatment. Abnormal ALT

for at least 6 months (12 months if HBeAg-negative) is the recommended criterion for study inclusion ([Sokal et al 2013](#)).

EASL guidelines and current clinical practice in adults recommend HBV DNA monitoring at least every 6 months during treatment with telbivudine. These guidelines also point out that virologic response (undetectable HBV DNA <300 copies/mL) at 24 weeks is associated with a lower incidence of resistance. Zoulim et al., reported that telbivudine treated adult patients with specific baseline characteristics (HBV DNA <9 $\log_{10}$  copies/mL and ALT  $\geq 2 \times$ ULN in HBeAg positive patients; HBV DNA <7 $\log_{10}$  copies/mL for HBeAg negative patients) and undetectable HBV DNA (<300 copies/mL) after 24 weeks of treatment had no resistance at Week 52 and very low resistance (2%) at Week 104 ([Zoulim et al 2012](#)). The stratification procedure will be used to achieve a distribution of approximately 80% of recruited patients with lower HBV DNA at screening (HBV DNA <9  $\log_{10}$  for HBeAg positive patients and with HBV DNA <7  $\log_{10}$  copies/mL for HBeAg negative patients).

EASL guidelines also recommend that in case of detectable HBV DNA at Week 24, telbivudine treated adults patients should be intensified with nucleotides (TDF or ADV). Currently none of the marketed nucleotides (tenofovir or adefovir) have an approved indication for pediatrics in the EU ([EASL 2012](#)). Therefore intensification is not an option in this trial and patients with HBV DNA  $\geq 300$  copies/mL (51 IU/mL) after 24 weeks of telbivudine treatment will be discontinued from study and handled at the discretion of treating physicians (see [Section 5.5.9](#)).

Based on treatment monitoring recommendation with telbivudine, treatment stopping rule has to be applied at Week 24. In addition, since patients on the placebo arm will be given the option of telbivudine treatment at Week 24, it is required to unblind patient's treatment after 24 weeks of treatment.

There is no indication for treatment of children in the “inactive HBsAg carrier” state which is characterized by undetectable or low HBV DNA and normal ALT levels ([Jonas et al 2010](#)). Following consultation with experienced CHB pediatricians, there is a clear consensus that HBeAg negative children are hardly eligible for antiviral treatment since most of them have low HBV DNA levels and normal ALT levels ([Jonas et al 2010](#)). Few patients are expected from this population and therefore the primary endpoint will be analyzed on the entire population including both HBeAg positive and negative patients.

Following Health authorities requirements, the study design has been agreed with the followings:

- HBeAg positive patients with HBV DNA  $> 5 \log_{10}$  copies/mL (or 20 000 IU/mL) and HBeAg negative with HBV DNA  $> 4 \log_{10}$  copies/mL (or 2 000 IU/mL), can be eligible (based on epidemiological survey (CLDT600A2414), 80% of patients with lower HBV DNA at screening are expected to be recruited).
- All patients with confirmed HBV DNA  $\geq 300$  copies/mL (51 IU/mL) after 24 weeks of telbivudine treatment will be discontinued from the study.

### 3.3 Rationale of dose/regimen, route of administration and duration of treatment

Single- and multiple-dose pharmacokinetics of telbivudine has been evaluated in healthy adults and in adults with chronic HBV infection. Telbivudine pharmacokinetics is similar in both populations. Telbivudine pharmacokinetics are dose proportional over the range of 25 mg to 1800 mg. Steady state is achieved after 5 to 7 days of once daily administration with an approximate 1.5-fold accumulation in systemic exposure. Inter-subject variability (CV %) for measures of systemic exposure (Cmax, AUC) was typically  $\leq 30\%$ . A pivotal bioequivalence study (NV-02B-025) showed that the FMI (final market image, 600-mg tablets) formulation is bioequivalent to the oral solution (30 mL x strength 20 mg/mL).

CLDT600A2104 was a single dose safety and pharmacokinetics study of telbivudine given as oral solution at either 15 or 25 mg/kg up to a maximum dose of 600 mg/day in HBsAg positive children aged 2 to  $< 18$  years. Extensive plasma PK samples (a total of 10 time points) were collected from each patient up to 120 hours post dosing. Twenty three children were enrolled and evaluated for safety, tolerability, and pharmacokinetic parameters. There were no significant safety issues identified in the study. Pharmacokinetic parameters in pediatric patients derived from study CLDT600A2104 along with the PK parameters obtained from a previous PK study (NV-02B-025) in healthy adults are summarized in [Table 3-1](#).

**Table 3-1 Comparison of PK parameters of telbivudine in Adults and Children by Age Groups**

PK parameters	n	Tmax (h)	Cmax (ng/mL)	AUC0-24h (ng.h/mL)	AUClast (ng.h/mL)	AUCinf (ng.h/mL)	T1/2 (h)
<b>CLDT600A2104 &gt;12-&lt; 18 years dosed with 600 mg oral solution</b>							
Mean	8	2.59	3510	22300	26800	27700	38.7
SD*		(1.97-4.00)	1190	5720	6590	6830	7.42
CV%			33.9	25.7	24.6	24.6	19.1
<b>CLDT600A2104 6-12 years dosed with 15 mg/kg oral solution</b>							
Mean	4	2.53	3290	17600	20700	21500	36.2
SD		(1.83-3.00)	748	3400	4550	4610	6.8
CV%			22.7	19.3	22.0	21.5	18.8
<b>CLDT600A2104 6-12 years dosed with 25 mg/kg oral solution</b>							
Mean	4	2.48	5430	33100	39700	40500	28.0
SD		(1.92-3.00)	1530	9530	9760	9680	7.03
CV%			28.2	28.8	24.6	23.9	25.1
<b>CLDT600A2104 2-&lt;6 years dosed with 15 mg/kg oral solution</b>							
Mean	6	2.00	2910	17900	21200	22100	29.9
SD		(1.28-3.03)	453	3550	4520	4760	10.5
CV%			15.6	19.8	21.3	21.6	35.2
<b>CLDT600A2104 2-&lt;6 years dosed with 25 mg/kg oral solution</b>							
Mean	1	4.00	2440	15300	19900	20400	28.3
<b>NV-02B-025 in adults dosed with 600 mg oral solution</b>							
Mean	23	3.00	3456	25437	30752	32440	43.8
SD		(2.00-6.00)	1170	7457	8032	8444	11.1

PK parameters	Tmax (h)	Cmax (ng/mL)	AUC0-24h (ng.h/mL)	AUClast (ng.h/mL)	AUCinf (ng.h/mL)	T1/2 (h)
CV%		33.9	29.3	26.1	26.0	25.3

\*Median and range are reported for Tmax

Compartmental analysis of the single dose data from the enrolled children was performed to predict the steady state exposure of telbivudine in pediatric patients based on the above PK data. Plasma telbivudine concentration versus time profiles for children aged 2 to 12 years administered a single 15 mg/kg dose of telbivudine and for children aged >12 to < 18 years administered a single 600 mg of telbivudine were fitted to a two-compartment 1<sup>st</sup> order, micro-constant, lag time, 1<sup>st</sup> order elimination PK model (WinNolin version 5.2). Following 20 mg/kg/day and 600 mg/day oral administration for children age 2 to 12 years and children age >12 to < 18 years, respectively, the model predicted systemic, steady state telbivudine exposures that closely matched those observed in healthy adults receiving 600 mg of telbivudine once daily. The summary predicted steady state pharmacokinetic parameters for all the children as compared to the target exposure in adults receiving the approved dose of 600mg/day, is presented in [Table 3-2](#).

**Table 3-2 Comparison of predicted LDT600 pharmacokinetics at the steady state in children age 2 to < 18 years to a historical study of healthy adults**

PK parameters	Dose	T <sub>max</sub> (h)	C <sub>max</sub> (ng/mL)	AUC <sub>0-24h</sub> (ng.h/mL)	C <sub>trough</sub> (ng/mL)
Adults <sup>a</sup>	600 mg/day	2 (1-4) <sup>b</sup>	3690±1250	26100±7200	200-300
Children (2 to 12 years)	20 mg/kg/day	2.10	3750±1120 <sup>c</sup>	28300±8490 <sup>c</sup>	268-280
Children (>12 to < 18 years)	600 mg/day	2.16	3340±1000 <sup>c</sup>	25070±7520 <sup>c</sup>	227-244

<sup>a</sup> All values from US label. <sup>b</sup> Mean (range).

<sup>c</sup> Estimation of SD based on typical inter-patient variability (CV 30%) for LDT600

The study result of a daily dose of 20 mg/kg for children was in the middle of the range predicted by comparing the telbivudine CL/F in children and adults based on previous experience with extrapolation of renally excreted nucleosides, such as lamivudine, from adults to children. In adults, a 600 mg dose (average 7.5 mg/kg) of telbivudine produces an AUC<sub>0-∞</sub> of approximately 23,000 ng/mL\*h (AUC<sub>0-24h</sub>, ~20,000 ng/mL\*h). To achieve similar exposures in children 2-6 years old, a weight-based dose of 21–27 mg/kg was predicted; for the 7–12 year age group a dose of 13–20 mg/kg was proposed. The full analysis with the final data on all 23 subjects agrees with the preliminary analysis that a dose of 20 mg/kg up to a total of 600 mg of telbivudine will result in similar exposure in children from age 2- < 18 years as observed in previous clinical studies conducted in adults receiving the marketed dose of 600 mg/day. This assessment is based on the plasma exposure results from all the children, the linear pharmacokinetics of telbivudine, and extrapolation of the data by standard pharmacokinetic modeling methods.

The prior relationship established in adults of telbivudine exposure and the antiviral activity at Week 4 ([Zhou et al 2006](#)) indicated a significant sigmoid-Emax exposure response relationship with 50% of maximal antiviral activity (EC50) at a steady state AUC<sub>0-t</sub> of 410+/-

140 ng\*h/mL. This is below the steady  $AUC_{0-t}$  of a 25mg daily dose. The maximal antiviral effect plateaued rapidly with 99.9% reduction in viral load ( $3 \log_{10}$ ) from baseline predicted at an  $AUC_{0-t}$  of 3360 ng\*h/mL which below the exposures achieved by a dose of 100 mg/day.

The comparable exposure of telbivudine in children to adults based on the pharmacokinetic data detailed above and the modeling is predicted at the recommended dosing of 20mg/kg up to a maximum of 600mg/day ([Table 3-2](#)). The exposure from the recommended dosing is expected to lead to the antiviral activity and safety established from the adult exposures. As noted in [Table 3-2](#) the variability in PK parameters is similar.

The current study has 2 year treatment duration, which has been agreed with Health Authorities in line with treatment guidelines as being the treatment period required for safety and efficacy evaluation in pediatrics.

### **3.4 Rationale for choice of comparator**

Out of the seven drugs approved worldwide for the treatment of CHB in adults (two forms of interferon (IFN alfa and peg-interferon alfa), and five nucleos(t)ide analogues (LAM, ADV, ETV, LDT and TDF)), none are currently approved in Europe for the treatment of children suffering from CHB. In the US, lamivudine is indicated for patients from 2-17 years of age, adefovir and tenofovir are labeled for children aged 12 years and older and common IFN -alfa is approved for use in children as young as 12 months of age.

No antiviral drug is approved worldwide to be used as control drug in an international multicenter phase III trial in pediatrics CHB patients. Therefore placebo will be used as comparator as agreed with European and US Health Authorities.

Placebo was used as a comparator in the pivotal phase III studies of IFN, LAM, ADV and TDF, as well as in most recent phase III study for other antiviral (ETV) treatments ([Sokal et al 1998](#); [Jonas et al 2002](#); [Jonas et al 2008](#); [Murray et al 2012](#)).

In the current study, the placebo arm is 6 months delayed treatment arm. All patients initially randomized to placebo will be provided with telbivudine treatment at Week 28 if they are still eligible for antiviral treatment at Week 24; patients not eligible for telbivudine treatment at Week 24 may start telbivudine treatment at a later visit until Week 52 based on investigator's decision and patient agreement.

### **3.5 Purpose and timing of interim analyses/design adaptations**

Interim analyses are planned for weeks 24 (primary analysis) and 52.

A DMC is planned to conduct regular safety data review for patient monitoring and where appropriate, to request and review additional safety and/or efficacy analyses (See [Section 8.4](#)). The DMC may request information on the current status of the study at any time according to their mission.

### 3.6 Risks and benefits

#### Benefits

The short-term benefits of antiviral therapy in children with CHB are to suppress viral replication, reduce liver inflammation, and reverse liver fibrosis, thereby protecting the liver. The long-term benefit is to reduce the risk of end stage liver disease including decompensated liver cirrhosis or hepatocellular carcinoma (HCC) ([Jonas et al 2010](#)). HBeAg negative patients would further benefit of antiviral treatment since they are generally associated with a more severe liver disease with a very low rate of spontaneous disease remission ([Marcellin et al 2005](#)). These are the anticipated short- and long-term benefits of telbivudine treatment for the patients in this study.

#### Risks Management

Currently telbivudine film-coated tablets have been approved for treatment of CHB in approximately 91 countries worldwide. Since the US launch in 2006 until 29-Feb-2012, the total worldwide exposure of telbivudine reached 329,556 PTY (patient treatment years) in adult CHB patients showing proven benefits without major safety concerns.

According to the 2012 EASL Guidelines ([EASL 2012](#)), resistance rates with telbivudine treatment are relatively low in patients with low baseline viremia ( $<9 \log_{10}$  copies/mL for HBeAg-positive and  $<7 \log_{10}$  copies/mL for HBeAg-negative patients), and who achieve undetectable HBV DNA ( $<300$  copies/mL) at 6 months of therapy.

In order to manage the risk of drug related resistance for the patients in this study, the following provisions have been made:

- After 24 weeks of telbivudine treatment, patients with confirmed HBV DNA  $\geq 300$  copies/mL (51 IU/mL) will be discontinued from the study and treated at the discretion of their investigators.
- Patients with primary non-response or virological breakthrough will be discontinued from the study and treated at the discretion of their investigators.
- Patients will be closely monitored to ensure good treatment compliance.

Among telbivudine treated patients in the GLOBE study, there were rare reports of myopathy (0.3%), all of which resolved after discontinuation of telbivudine ([Lai et al 2007](#)). This risk of muscle related events will be managed in this study through close monitoring and the use of a muscle symptom management algorithm for children and adolescents. The algorithm will provide guidance for patient management including drug discontinuation criteria.

A common laboratory abnormality observed in previous clinical studies was an increase in serum creatine kinase (CK) levels with 7.5% of patients having Grade 3 or 4 CK elevations within 1 year of treatment. Most CK elevations were asymptomatic and CK values typically decreased by the next visit on continued treatment. Baseline or on-treatment CK elevation does not predict myopathy ([Dong et al 2011](#)). Treatment was rarely interrupted or discontinued as a result of elevated CK. CK levels in this study will be closely monitored ([Lai et al 2007](#); [Liaw et al 2009](#)). More details can be found in the [Investigator Brochure](#).

The risk to subjects in this trial will be minimized by ongoing DMC data review, compliance with the inclusion/exclusion criteria, close clinical monitoring and treatment stopping rules, close safety monitoring including CK and muscle symptoms and the 24 weeks placebo treatment period with a planned full analysis once all patients have completed their Week 24 visit. Using all the above considerations and measurements, potential risks to patients will be minimized to ensure patient's benefits and risks maintained at a favorable level.

All other known classical adverse events related to anti-HBV nucleos(t)ide analogues (including peripheral neuropathy, ALT flare, lactic acidosis, acute pancreatitis and hypersensitivity reactions) will be monitored and reported in this study following the normal AE / SAE process.

## 4 Population

The study population will be comprised of male or female patients between 2 and <18 years of age (at the time of randomization), with HBeAg-positive and HBeAg-negative CHB and compensated liver disease. In the Republic of South Korea, children aged 2 years to < 12 years (at the time of randomization) only will be enrolled. It is planned to randomize at least 150 patients from multiple centers worldwide. Age inclusion criteria limits apply to the study subject's age at time of randomization.

### 4.1 Inclusion criteria

Patients eligible for inclusion in this study have to fulfill **all** of the following criteria:

1. A signed informed consent / assent must have been obtained from both parents or legal guardian(s) before any assessment is performed.
2. Male or female out-patients between 2 and < 18 years of age (at time of randomization), except in the Republic of South Korea, where children aged 2 years to < 12 years only (at time of randomization) will be enrolled.
3. Clinical history compatible with compensated chronic hepatitis B.
4. Documented compensated chronic hepatitis B defined by the following:
  - a Positive serum HBsAg at screening and at least one other documentation of HBsAg positive at least 6 months prior to screening
  - b For HBeAg positive patients at screening, significant biologic signs of disease activity following EASL guidelines recommendations for CHB pediatric patients ([Sokal et al 2013](#))
    - i) serum HBV DNA level  $\geq 5 \log_{10}$  copies/mL (COBAS Taqman<sup>®</sup>) (or 20 000 IU/mL) at screening as assessed by central laboratory and
    - ii) serum ALT  $\geq 1.5 \times \text{ULN}$  and  $< 10 \times \text{ULN}$  (pediatric ULN) either once during the screening period or twice (2 times) within 6 months prior to screening
  - c For HBeAg negative patients at screening, significant biologic signs of disease activity following EASL guidelines recommendations for CHB pediatric patients ([Sokal et al 2013](#))
    - i) serum HBV DNA level  $\geq 4 \log_{10}$  copies/mL (COBAS Taqman<sup>®</sup>) (or 2 000 IU/mL) at screening as assessed by central laboratory and

- ii) serum ALT  $\geq 1.0 \times \text{ULN}$  and  $< 10 \times \text{ULN}$  (pediatric ULN) either once during the screening period or twice (2 times) within 12 months prior to screening
- 5. Patients and parent (or legal guardian) are willing to comply with the study drug regimen and all other study requirements.
- 6. Patient meeting criteria for treatment according to local guidelines.

#### **4.2 Exclusion criteria**

Patients fulfilling **any** of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

- 1. Use of other investigational drugs within 5 half-lives of enrollment, or within 30 days, whichever is longer.
- 2. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes.
- 3. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases. Patients, who have ultrasonographic findings of hepatic mass and/or elevated AFP suggestive of possible HCC prior to enrollment, should have the disease ruled-out prior to entrance into the study.
- 4. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive HCG laboratory test.
- 5. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant unless they are using effective methods of contraception during dosing of study treatment and up to 12 days after stopping study treatment.

Effective contraception methods 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.

- 6. Sexually active adolescent males who do not agree to use a condom during intercourse while taking drug and for 12 days after stopping medication to fathering a child in this period; by vasectomized adolescent male patients who do not agree to condom use in order to prevent delivery of the drug via seminal fluid.

7. Patients with acute or chronic infection of HCV, HDV, HIV, or with acute infection of HAV, HEV, CMV or EBV.
8. Patient has received treatment of interferon or any other immunomodulatory agents within the last 12 months prior to screening.
9. Patient has received treatment of any nucleoside or nucleotide drugs or other anti -CHB treatment (approved or investigational) at any time before screening.
10. Patient has a medical condition that requires frequent use of systemic acyclovir or famciclovir, systemic corticosteroids (topical and inhaled corticosteroids are allowed).
11. Patient has decompensated liver disease defined as a Child-Turcotte-Pugh (CTP) Score  $\geq 7$  (Class B or C).
12. Patient has one or more additional known primary or secondary causes of liver disease, other than infectious agents, including alcoholic or non-alcoholic liver disease, fatty liver, hepatobiliary disease, Wilson disease and alpha-1 antitrypsin deficiency, Gilbert's syndrome, Dubin-Johnson syndrome etc.
13. Liver transplant recipients. Organ or bone marrow transplant recipients.
14. Patient is currently abusing illicit drugs, or has a history of illicit substance abuse.
15. All patients are required to be abstinent from alcohol during the course of the study otherwise excluded.
16. Patient has a medical condition requiring the chronic or prolonged use of potentially hepatotoxic drugs or nephrotoxic drugs or chemotherapy.
17. History of any other acute or chronic medical condition (including congenital diseases, metabolic diseases, malignant diseases, neurological disorders, nephrotic diseases, pancreatitis, autoimmune disorders, diabetes, etc.) that in the opinion of the investigator would make the patient unsuitable for inclusion into the study.
18. Patient has a history of myopathy, myositis, persistent muscle weakness or persistent high serum CK levels ( $\geq 7 \times \text{ULN}$ ), 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).
19. Patients receiving any drugs potentially associated with myopathy (e.g chloroquine, hydroxychloroquine, HMGCoA redutase inhibitors, fibric acid derivatives, penicillamine, zidovudine, cyclosporine, erythromycin, niacin, azole antifungals, etc.) within 3 months prior to screening.
20. Any other clinical significant disease, condition or abnormality, unrelated to their HBV infection at screening, as assessed by the investigator, including:
  - Hemoglobin  $< 11 \text{ g/dL}$  ( $110 \text{ g/L}$ ) for males or  $< 10 \text{ g/dL}$  ( $100 \text{ g/L}$ ) for females
  - Total WBC  $< 3,500/\text{mm}^3$  ( $3.5 \times 10^9/\text{L}$ )
  - Absolute neutrophil count (ANC)  $< 1,500/\text{mm}^3$  ( $1.5 \times 10^9/\text{L}$ )
  - Platelet count  $< 120,000/\text{mm}^3$  ( $120 \times 10^9/\text{L}$ )
  - Prothrombin time prolonged by more than 3 seconds (based on ULN; of the reference value); or INR  $> 1.5$

- Serum amylases or lipase  $\geq 1.5 \times \text{ULN}$
- Serum albumin ( $< 3.5 \text{ g/dL}$ ); ( $< 35 \text{ g/L}$ )
- Total bilirubin ( $\geq 2 \times \text{ULN}$ )
- estimated GFR  $< 50 \text{ mL/min}$  using Schwartz formula
- Serum phosphate  $< 1.5 \text{ mg/dL}$

All the above laboratory parameters need to consider age adjusted ULN changes.

If selected patients meet all other eligibility criteria, patients with a single laboratory value outside of the allowable range, may be considered eligible for enrolment, as long as that abnormal lab value is within 10% of the allowable value.

No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

## 5 Treatment

### 5.1 Protocol requested treatment

#### 5.1.1 Investigational treatment

The following study medication will be supplied to the sites:

- LDT600 (telbivudine, manufactured by Novartis) oral solution (20mg/mL) will be used as a dosage of 20 mg/kg
- LDT600 (telbivudine, manufactured by Novartis) 600 mg film-coated tablets
- Placebo to LDT600 oral solution
- Placebo to LDT600 film-coated tablets

Formulation, dose and frequency of administration by patient age are detailed in [Table 5-1](#)

#### 5.1.2 Additional study treatment

No additional treatment beyond investigational treatment is requested for this trial.

### 5.2 Treatment arms

Patients will be assigned to one of the two treatment arms in a ratio 5:1

#### Arm 1: Telbivudine:

- Any age and weight  $< 30 \text{ kg}$ : telbivudine oral solution (20mg/mL): 20 mg/kg up to 600 mg q.d, corresponding to weight (kg) x 1ml, p.o. once daily
- $< 12 \text{ years old}$  and weight  $\geq 30 \text{ kg}$ : telbivudine oral solution (20mg/mL): 600 mg/day corresponding to 30 mL p.o. once daily
- $\geq 12 \text{ years old}$  and weight  $\geq 30 \text{ kg}$ : telbivudine film-coated tablet 600 mg/day, corresponding to 1 tablet p.o. once daily

#### Arm 2: Placebo:

- Any age and weight < 30kg: placebo oral solution corresponding to weight (kg) x1mL, p.o. once daily
- < 12 years old and weight  $\geq$  30kg: placebo oral solution corresponding to 30 mL p.o. once daily,
- $\geq$  12 years old and weight  $\geq$  30kg: placebo tablet, corresponding to 1 tablet p.o. once daily.

### **Eligibility criteria for placebo treated patients to start telbivudine treatment at week 28**

1. Positive serum HBsAg at baseline and at Week 24
2. For HBeAg positive patients:
  - a. Serum HBV DNA level  $\geq$  5  $\log_{10}$  copies/mL (COBAS Taqman<sup>®</sup>) (or 20 000 IU/mL) at Week 24 (visit 6) as assessed by central lab
3. For HBeAg negative patients:
  - a. Serum HBV DNA level  $\geq$  4  $\log_{10}$  copies/mL (COBAS Taqman<sup>®</sup>) (or 2 000 IU/mL) at Week 24 (visit 6) as assessed by central lab

Placebo patients who are not eligible for telbivudine treatment at week 28 may start telbivudine at a later visit until Week 52. The similar eligibility criteria will be used.

### **5.3 Treatment assignment**

At Visit 2, all eligible patients will be randomized via Interactive Voice Response System (IVRS/IWRS) to one of the treatment arms. The investigator or his/her delegate will contact the IVRS/IWRS after confirming that the patient fulfills all the inclusion/exclusion criteria. The IVRS/IWRS will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of study drug to be dispensed to the patient. The randomization number will not be communicated to the caller.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the IVRS/IWRS provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing each of the study drugs.

Randomization will be stratified by age group (age at baseline (visit 2)) and by HBV DNA level (screening value, available at the time of baseline visit (visit 2)). Patients will be randomized to treatment arm 1 (telbivudine) or treatment arm 2 (placebo) in a ratio 5:1.

Stratification at baseline is done to balance the number of patients randomized to telbivudine or placebo within the levels of stratification factors. Patients will be stratified into 6 strata: three age groups and the HBV DNA status (low and high) where HBV DNA low is  $<9 \log_{10}$  copies/mL for HBeAg positive patients and  $<7 \log_{10}$  copies/mL for HBeAg negative patients.

Approximately 80% of patients with lower HBV DNA at screening (i.e. for HBeAg positive patients HBV DNA  $<9$  log<sub>10</sub> and HBeAg negative patients with HBV DNA  $<7$  log<sub>10</sub> copies/mL) are expected to be recruited.

Subsets of patients by age (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

The randomization scheme for patients will be reviewed and approved by Novartis Randomization Office.

## **5.4 Treatment blinding**

The total double-blind treatment period will be 24 weeks.

Patients, investigator staff, persons performing the assessments, and data analysts will remain blind to the identity of the treatment from the time of randomization until Week 24 (visit 6), using the following methods: (1) Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study with the following exceptions: expert pharmacokineticists will be unblinded and will have access to the randomization list in order to analyze the PK samples in a timely manner; (2) the identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, appearance, taste and odor. Specific laboratory assessments (HBV DNA and ALT) will be blinded for patients, investigator staff, persons performing the assessments, and data analysts in order to remain blinded to the identity of the treatment from the time of randomization until Week 24. Alert messages will be received by investigator staff to ensure safety monitoring of the patients during this period.

Unblinding will only occur in the case of patient emergencies (see [Section 5.5.12](#)) or on request by the Data Monitoring Committee.

At Week 24 (visit 6), all patients will be unblinded and HBV DNA level will be assessed. The therapeutic decision will be taken for all patients at Week 28, based on Week 24 assessments.

## **5.5 Treating the patient**

### **5.5.1 Patient numbering**

Each patient is uniquely identified in the study by a combination of his/her center number and patient number. The center number is assigned by Novartis to the investigative site. Upon signing the informed consent form, the patient is assigned a patient number by the investigator. At each site, the first patient is assigned patient number 1, and subsequent patients are assigned consecutive numbers (e.g. the second patient is assigned patient number 2, the third patient is assigned patient number 3). The investigator or his/her staff will contact the IVRS/IWRS and provide the requested identifying information for the patient to register them into the IVRS/IWRS. Only the assigned patient number should be entered in the field labeled



“Patient ID” on the EDC data entry screen (e.g. enter ‘1’, ‘2’, etc.) Once assigned to a patient, the patient number will not be reused. If the patient fails to be randomized for any reason, the IVRS/IWRS must be notified within 2 days that the patient was not randomized. The reason for not being randomized will be entered on the Screening Log, and the Demography CRF pages should also be completed.

### **5.5.2 Dispensing the study treatment**

Each study site will be supplied by Novartis with study drug in packaging of identical appearance. LDT600 (telbivudine, manufactured by Novartis) oral solution (20mg/mL) will be identical in appearance to the Placebo to LDT600 oral solution, and the LDT600 (telbivudine, manufactured by Novartis) 600mg film-coated tablets will be identical in appearance to the Placebo to LDT600 film-coated tablets.

The investigational treatment packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to one of the 2 treatment arms and active or placebo treatment. Investigator staff will contact IVRS/IWRS to obtain the medication number (s) to be dispensed to the patient, either active or placebo. Immediately before dispensing the package to the patient, investigator staff will complete the label indicating the patient randomization number, will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient’s unique patient number.

### **5.5.3 Handling of study treatment**

#### **5.5.3.1 Handling of investigational treatment**

Study treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. Upon receipt, all study drugs should be stored according to the instructions specified on the drug labels. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CPO Quality Assurance.

- Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the drug, but no information about the patient except for the medication number.
- The investigator must maintain an accurate record of the shipment and dispensing of investigational treatment in a drug accountability log. Monitoring of drug accountability will be performed by the field monitor during site visits and at the completion of the trial. Patients will be asked to return all unused investigational treatment and packaging at the end of the study or at the time of discontinuation of investigational treatment.
- At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused investigational treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

### 5.5.3.2 Handling of other study treatment

Not applicable.

### 5.5.4 Instructions for prescribing and taking study treatment

Investigator staff will instruct the patients to take the medication orally every morning either with or without food. The investigator should instruct the patient to take the study drug exactly as prescribed.

The tablets should be taken as whole and must not be divided for dose adjustment purposes. The oral solution intake should follow the instructions as described in the oral dispensing instructions.

The first dose of study medication will be taken on Baseline (Day 1) under the supervision of the study nurse. Dosing will be continued for 104 weeks until the Week 104 study visit unless treatment discontinuation is required or patient withdraws from the study ([Section 5.5.9](#)).

For two visits on Week 4 and 24, each patient will be required to come to the clinic before taking LDT600 on that day for a blood sample to measure a trough (pre-dose) level. After collecting the trough sample, LDT600 will be taken by mouth in the clinic ([Section 6.6.3](#)).

**Table 5-1 Study medication assignment and dosage**

Patient age	Patient weight	Formulation	Dosage	Amount/day
Any age	Weight < 30kg	oral solution telbivudine 20mg/mL or placebo solution	20 mg/kg up to 600 mg q.d.	Weight (kg) x 1 mL
< 12 years old	Weight ≥ 30kg	oral solution telbivudine 20mg/mL or placebo solution	600 mg/day	30 mL
≥ 12 years old	Weight ≥ 30kg	film-coated tablet telbivudine 600 mg or placebo tablet	600 mg/day	1 tablet

Patients who will have their 12<sup>th</sup> birthday during the 24-week double-blind treatment period will continue receiving the oral solution until the end of the 24-week period. Afterwards these patients will be provided with the opportunity to change treatment formulation from oral solution to tablet only every half year after Week 24 double-blind treatment period (i.e. at Week 52, 76 and 104) if body weight increase ≥30kg.

The patient should be instructed to contact the investigator if he/she is unable for any reason to take the study drug as prescribed. Patients' ≥12 years old and weight ≥30kg that are unable to swallow the tablets can be switched to oral solution (IRT call required).

All kits of investigational treatment assigned by the IRT will be recorded/databased in the IRT. The investigator should promote compliance by instructing the patient to take the study treatment exactly as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient should be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed.

### Week 24 unblinding and instructions for taking study treatment

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

Patients randomized to treatment arm 1 (telbivudine):

- Patients with HBV DNA <300 copies/mL (51 IU/mL) at Week 24 will remain on telbivudine treatment until Week 104.
- Patients with confirmed HBV DNA ≥300 copies/mL (51 IU/mL) at Week 24 will be discontinued from study at the next visit (Week 28) as described in [Section 5.5.9](#).

Patients randomized to treatment arm 2 (placebo):

- Treatment eligibility will be confirmed using Week 24 (visit 6) assessments (see [Section 5.2](#)) and eligible patients will initiate antiviral treatment with telbivudine at Week 28 (visit 7). At Week 52 (visit 9, which represents 24 weeks of telbivudine treatment for this group of patients), HBV DNA level will be assessed:
  - Patients with HBV DNA <300 copies/mL (51 IU/mL) at Week 52 will remain on telbivudine treatment until last on-treatment study visit (Week 104);
  - Patients with confirmed HBV DNA ≥300 copies/mL (51 IU/mL) at Week 52 will be discontinued from study as described in [Section 5.5.9](#).
- Placebo randomized patients who are non-eligible for telbivudine treatment at Week 24, may continue in the study until Week 52 and may start telbivudine treatment at a later visit until Week 52 based on investigator's decision and patient agreement.

### **5.5.5 Permitted dose adjustments and interruptions of study treatment**

Study drug interruptions are not permitted.

### **5.5.6 Rescue medication**

No rescue antiviral therapy will be provided. In the event of discontinuation of investigational treatment for insufficient therapeutic effect or viral breakthrough, or for ALT flare upon study completion at Week 104, the patient may be treated by the investigator according to local practice. The reason for discontinuation of investigational treatment and any intervention will be clearly described in the CRF (e.g., for insufficient therapeutic effect, safety).

### **5.5.7 Concomitant treatment**

The investigator should instruct the patient to notify the study site about any new medications he/she takes after the start of the study drug. All medications and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient was enrolled into the study must be listed on the Concomitant medications/Significant non-drug therapies into the CRF.

### **5.5.8 Prohibited treatment**

Use of the treatments displayed in [Table 5-2](#) is NOT allowed after the start of study treatment. These drugs will either confound the efficacy or safety of the study, or they have potential drug-drug interaction with the study drug. In addition any drugs which has any known or potential risks for pediatrics population in terms of growth, bone, liver, neurological system etc. are strictly prohibited in this study.



Investigators need to guide the patients not to take any prohibited medication. In case they are used and they cause hepatotoxicity or nephrotoxicity, investigators also need to monitor the relevant organic function ([Table 5-2](#)).

For the patient's safety, it is within the Investigator's responsibility to carefully educate the patient about prohibited medication and compliance to study medication.

**Table 5-2      Prohibited treatment**

Medication	Action to be taken
Any drug which has any known or potential risks for pediatrics population in terms of growth, bone, liver, neurological system etc are strictly prohibited in this study	Stop the prohibited drug immediately otherwise patients will be discontinued from the study
Any other investigational drug LAM, ADV, ETV, TDF, FTC, etc.	Stop prohibited treatment; monitor relevant ADR Stop prohibited treatment; monitor ALT, HBV DNA, etc.
Systemic use of Acyclovir, famciclovir	Stop prohibited treatment if taken > 10d over 3 months
IFNs, Thymosin, interleukins, any immune modulator	Stop prohibited treatment; monitor ALT, AST, relevant ADR
Systemic corticosteroids	Stop prohibited treatment; monitor CK, ALT, AST, relevant ADR
Hepatotoxic drugs (dapsone, erythromycin, systemic azole antifungals, anti-tuberculosis drugs, toxic dose of acetaminophen/paracetamol, herbal medications)	Stop prohibited treatment; monitor ALT, AST, TB, Alb, PT, etc.
Nephrotoxic drugs (aminoglycosides, amphotericin B, foscarnet, vancomycin, cyclosporine, tacrolimus, frequent use of NSAIDs or aspirin)	Stop prohibited treatment; monitor GFR, creatinine, cystatin C, urinalysis
Chemotherapy drugs for malignant diseases or immune-suppressive therapy for transplantation	Stop prohibited treatment or discontinue from study treatment; monitor GFR, WBC, RBC, ALT, AST, TB.
Alcohol abuse	Stop alcohol consumption for all pediatrics patients during the study period
Illicit drug abuse	Stop illicit drug abuse; monitor relevant ADR
Drugs associated with myopathy (Chloroquine, hydroxychloroquine, HMGCoA reductase inhibitors, fibric acid derivatives, penicilamine, zidovudine, cyclosporine, erythromycin, niacin, azole antifungals, etc)	Stop prohibited treatment immediately otherwise discontinued from the study treatment; monitor CK, muscle symptoms, muscle strength, etc.

If prohibited treatment is taken and the actions as given in the table above ([Table 5-2](#)) are not followed, patients have to be discontinued from the study ([Section 5.5.9](#)). The following list of medications can only be administered under certain circumstances or is restricted by a maximum dose or duration. However, new medications for study patients should be initiated with caution, since they may increase the onset of adverse events. All concomitant medications will be captured on the concomitant medication CRF with the indication for use documented.

- Short term use of systemic acyclovir or famciclovir defined as periods of less than 10 days over 3 months is allowed.
- Topical and inhaled corticosteroids are permitted.
- Less than one week use of NSAID (e.g. aspirin, paracetamol / acetaminophen, and ibuprofen) at the recommended dose intended for anti-inflammatory therapy is permitted (see [Appendix 6](#) for the recommended dosage of paracetamol / acetaminophen).
- If medically necessary, treatment with non-hepatotoxic medications is allowed.

Predefined vaccination plan (except for HBV) for the subjects is recommended to be continued during the study. All the history vaccinations taken by the pediatrics are needed to be collected in the screening; and each new vaccination subjects taken during the study need be recorded in the study with the vaccine name, dosage, date, and adverse reactions.

Herbal medications will be allowed except for those that cause known hepatotoxicity or muscle toxicity. All herbal medications will be captured on the concomitant medication CRF as “herbal supplement” with the indication for use documented.

### **5.5.9 Discontinuation of study treatment and premature patient withdrawal**

Patients and parents (or legal guardian) may voluntarily discontinue treatment for any reason at any time.

The investigator should discontinue study treatment for a given patient and/or withdraw the patient from study if, on balance, he/she believes that continuation would be detrimental to the patient's well-being.

Study treatment must be discontinued under the following circumstances:

- Emergence of the following adverse events:
  - a. Patient has clinical signs/symptoms of hepatic decompensation (Child-Pugh B or C)
  - b. Severe ALT flare on treatment ([Glossary of terms](#))
  - c. ALT  $> 3 \times$  ULN and  $> 2 \times$  baseline **AND** (TBiL  $> 2 \times$  ULN or INR  $> 1.5$ )
  - d. Patient is diagnosed with cancer (other than basal cell or squamous cell carcinoma) including but not limited to HCC
  - e. Patients experiencing muscle related symptoms as indicated in [Section 7.7](#)
  - f. Patient co-infected with HCV, HDV or HIV. If patient is co-infected with HAV, HEV, CMV, or EBV during the study, patient disposition will be at the investigator's discretion based on the severity of the other virus infection.
  - g. Any adverse event that could affect physical growth
- Any laboratory abnormalities that, according to the investigator opinion, might affect study treatment (e.g eGFR  $< 50$  mL/min)
- Pregnancy
- Withdrawal of informed consent
- The following deviations from the prescribed dose regimen for study treatment:
  - a. Patients receiving telbivudine treatment and with HBV DNA  $\geq 300$  copies/mL (51 IU/mL) at Week 24 (see [Section 3.1](#))

- b. unplanned treatment unblinding in the case of patient emergencies as judged by the treating physician
- Use of prohibited treatment as per [Table 5-2](#).
- Any other protocol deviation that results in a significant risk to the patient's safety

The appropriate personnel from the site and Novartis will assess whether study treatment should be discontinued for any patient whose treatment code has been broken inadvertently for any reason. The investigator must contact the IRT to register the patient's discontinuation from study treatment.

Patient discontinued from study treatment should complete the End of Treatment visit and the 12-weeks safety follow-up visit. Post-treatment observation ceases either at 12-weeks post treatment follow-up visit or at the time of an alternative anti-HBV therapy is initiated before the 12-weeks safety follow-up visit.

These changes must be recorded on the Dosage Administration Record CRF.

### **Management of primary non-responder at Week 24**

Primary response is defined as HBV DNA reduction of  $\geq 1 \log_{10}$  copies/mL (1 log<sub>10</sub> IU/mL) at Week 12 on treatment compared with baseline and confirmed at the next visit (Week 16).

Good compliant patients with a HBV DNA reduction at Week 12 of  $< 1 \log_{10}$  copies/mL compared with baseline and confirmed at the next visit (Week 16), meet the diagnosis criteria of Primary Non-Response (PNR). When the study treatment code is unblinded for all patients at Week 24, those patients identified as PNR but who have achieved a satisfactory viral response (HBV DNA  $< 300 \log_{10}$  copies/mL) at week 24 (confirmed at week 28) will be allowed to continue study treatment; those patients identified as PNR and who have a HBV DNA levels  $\geq 300 \log_{10}$  copies/mL will be discontinued from the study treatment at Week 28 and managed at the discretion of the investigators.

### **Management of telbivudine patients with HBV DNA $\geq 300$ copies/mL (51 IU/mL) at Week 24**

Patients with confirmed HBV DNA  $\geq 300$  copies /mL (51 IU/mL) after 24 weeks of telbivudine treatment will be discontinued from the study treatment and managed at the discretion of the investigators.

For patients with HBV DNA  $\geq 300$  copies /mL (51 IU/mL) at Week 24 for the first occurrence after achieving initial response ( $< 300$  copies/mL (51 IU/mL)) prior to Week 24, a confirmatory value (HBV DNA  $\geq 300$  copies/mL (51 IU/mL)) should be obtained at Week 26 (unscheduled visit) before discontinuation.

### **Management of patients with virological breakthrough and/or genotypic resistance after Week 24**

Virological breakthrough will be assessed in real time during the study. In case of confirmed VB, genotypic resistance testing should be performed. Patients who develop VB (confirmed) or genotypic resistance after 24 weeks of telbivudine treatment will be discontinued from the study treatment and will be managed at the discretion of the investigators.



### **Management of patients with “complete response”**

Complete response is defined as HBV DNA <300 copies/mL (51 IU/mL), HBeAg seroconversion and ALT normalization. Patients with confirmed complete response 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.

Patients initially randomized to placebo at baseline and treated with telbivudine at Week 28 or at later visits will be managed similarly.

#### **5.5.10 Withdrawal of consent**

Patients and parents (or legal guardian) may voluntarily withdraw consent to participate in the study for any reason at any time.

Withdrawal of consent occurs only when a patient does not want to participate in the study anymore and does not want any further visits or assessments and does not want any further study related contacts and does not allow analysis of already obtained biologic material.

If a patient withdraws consent, the investigator must make every effort to determine the primary reason for this decision and record this information. Study treatment must be discontinued and no further assessments conducted. All biological material that has not been analyzed at the time of withdrawal must not be used. Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up.

#### **5.5.11 Loss to follow-up**

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be considered lost to follow-up until his/her scheduled end of study visit would have occurred.

#### **5.5.12 Emergency unblinding of treatment assignment**

Emergency treatment code breaks should only be undertaken when it is essential to treat the patient safely and efficaciously. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a patient, he/she must provide the requested patient identifying information and confirm the necessity to break the treatment code for the patient. The investigator will then receive details of the investigational drug treatment for the specified patient and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the Global Trial Leader (GTL) that the code has been broken.

It is the investigator's responsibility to ensure that there is a procedure in place to allow access to the IRT in case of emergency. The investigator will inform the patient how to contact

his/her backup in cases of emergency when he/she is unavailable. The investigator will provide protocol number, study treatment name if available, patient number, and instructions for contacting the local Novartis CPO (or any entity to which it has delegated responsibility for emergency code breaks) to the patient in case an emergency treatment code break is required at a time when the investigator and backup are unavailable.

An assessment will be done by the appropriate site personnel, the Global Trial Leader and the Novartis Medical Specialist after an emergency treatment code break to assess whether or not study/investigational treatment should be discontinued for a given patient ([Section 5.5.9](#)).

### **5.5.13 Study completion and post-study treatment**

Study completion is defined for an individual patient who meets the screening requirements, attends the Baseline Day 1 visit, and completes the 104 weeks treatment phase of the study and 12 weeks post-treatment safety follow-up phase of the study.

The study recruitment is completed when at least 150 patients have been randomized to the treatment arms. Patients already in screening at the time of enrollment completion (i.e. when 150 patients have been randomized) should be allowed to enter the study if they meet all of the inclusion/exclusion criteria.

Patients who complete the study treatment period enter into the 12 weeks post-treatment follow-up phase (also called Safety Follow-up). It is up to the investigator's discretion to decide on the requirement of additional HBV treatment based on local practice guidelines after study completion. The Sponsor will make all effort to supply post-study provision of telbivudine until marketing authorization is received, as permitted by local law and regulation and if patients who have responded to treatment with telbivudine may benefit from ongoing treatment after the end of treatment visit (Week 104) as determined by the investigator. Any HBV treatment prescribed for the post-treatment follow-up phase must be recorded as concomitant medication.

The investigator must provide follow-up medical care for all patients who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care.

### **5.5.14 Early study termination**

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and treated for a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

## **6 Visit schedule and assessments**

[Table 6-1](#) lists all the assessments from the Screening period until the Safety follow-up visit and it is indicated with an "X" when each assessment has to be performed. Informed consent / assent will be collected from all patients prior to entering into the Screening period ([Section 10.2](#)). Patients can be randomized as soon as all screening evaluations and results are available and eligibility confirmed. Patients, who have disqualified parameters for HBV

related markers, biochemistry or hematology at screening visit, can be considered for re-test every 3 months within a period of 6 months of initial screening.

Patients should be seen for all visits on the designated day, a  $\pm$  7 day window is recommended.

Patients who discontinue study treatment before completing the study, and those who prematurely withdraw from the study for any reason, should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the visit 13 (Week 104) will be performed. A 12-weeks safety follow-up visit should be completed. Post-treatment observation ceases either at 12-weeks post-treatment follow-up visit or when alternative anti-HBV therapy is started.

**Table 6-1** **Assessment schedule**



Study Phase	Screen Period	Baseline	Treatment Weeks Post-baseline												Safety follow-up <sup>3</sup>
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13 <sup>2</sup>		14
Week	-10 weeks prior to BL <sup>1</sup>	Day 1	4	12	16	24	28 <sup>4</sup>	40	52	64	76	88		104 End of Treatment or SDD/PPW	116 End of Study or - 12 weeks post treatment
Vaccination records	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Compliance Questionnaire			x	x	x	x	x	x	x	x	x	x	x	x	
Muscle management algorithm <sup>15</sup>			As applicable in case of muscle event												
Dispense telbivudine or placebo		x	x	x	x	x <sup>17</sup>	x <sup>4</sup>	x	x <sup>18</sup>	x	x	x			

Study Phase	Screen Period	Baseline	Treatment Weeks Post-baseline												Safety follow-up <sup>3</sup>
			3	4	5	6	7	8	9	10	11	12	13 <sup>2</sup>		
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13 <sup>2</sup>	14	
Week	-10 weeks prior to BL <sup>1</sup>	Day 1	4	12	16	24	28 <sup>4</sup>	40	52	64	76	88	104 End of Treatment or SDD/PPW	116 End of Study or - 12 weeks post treatment	

<sup>10</sup> Patients on telbivudine with HBV DNA  $\geq$ 300 copies/mL (51 IU/mL) will be discontinued at the next visit

<sup>11</sup> Screening is a serum pregnancy test for patients with child bearing potential only, all following ones are urine tests

<sup>12</sup> Including hemoglobin (Hgb), hematocrit (Hct), red blood cell count, white blood cell count (WBC) and differential and platelet count

<sup>13</sup> Including specific gravity, pH, protein, glucose, blood, [REDACTED]

<sup>15</sup> Only applicable to patients who follow the Muscle Symptom Algorithm. It includes Muscle strength test, muscle symptom questionnaire and muscle pain score assessment. [REDACTED]

<sup>17</sup> Patients treatment to be unblinded, eligible patients on placebo to start telbivudine treatment at Week 28

<sup>18</sup> Patients randomized to placebo with HBV DNA  $\geq$ 300 copies/mL (51 IU/mL) at Week 52 to discontinue treatment

<sup>19</sup> Virology screening (Anti-HIV-1+2, Anti-HCV, Anti-HDV, Anti-HAV IgM, Anti-HEV IgM, Anti-EBV IgM & IgG to Viral Capsid Ag, Anti-CMV IgM and IgG)

<sup>20</sup> If an ultrasound was performed during the month prior to screening it is not necessary to obtain one during the screening period.

## **6.1 Information to be collected on screening failures**

All patients who have signed informed consent but not entered into the next study phase will have the study completion page for the screening period, demographics, inclusion/exclusion, and SAE data collected in the CRF pages. Adverse events that are not SAEs will be followed by the investigator and collected only in the source data.

Investigators will have the discretion to record abnormal test findings on the medical history CRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

## **6.2 Patient demographics/other baseline characteristics**

At the screening visit, patient demographic and baseline characteristic data to be collected on all patients include: date of birth, age, sex, race, ethnicity, child-bearing potential, origin of HBV infection and source of patient referral.

The screening period should not exceed 10 weeks.

Relevant medical history/current medical condition data includes data until the start of study drug (at the baseline visit). Where possible, diagnoses will be recorded and not symptoms.

Furthermore, the following will be assessed at the screening and / or baseline visits:

- Complete physical examination at baseline visit only
- Vital signs
- Body height and weight
- Tanner staging assessment for age group 2 (from 6 to less than 12 years old) and age group 3 (from 12 to less than 18 years old) at baseline visit only
- Virology screening (at screening visit only): Anti-HIV1+2, Anti-HCV, Anti-HDV, Anti-HAV IgM, Anti-HEV IgM, Anti-EBV IgM & IgG to Viral Capsid Ag and Anti-CMV IgM and IgG
- AFP, PT, amylase and lipase levels
- HBeAg/HBeAb and anti-HBc
- HBsAg/HBsAb
- HBV DNA level
- Pregnancy test (serum pregnancy test for patients with child bearing potential only at screening, urine pregnancy test at baseline)
- Hematology (hemoglobin, hematocrit, red blood cell count, white blood cell count and differential and platelet count)
- Biochemistry (ALT, AST, ALP, creatinine, CK, cystatin C, blood glucose, phosphate, total Bilirubin, Albumin)
- Urinalysis (specific gravity, pH, protein, glucose, blood, WBC, RBC sediments, proteinuria, urine creatinine and phosphates)

- Abdominal B-Ultra Sound at screening visit; if an abdominal B-US has been performed during the month prior to screening, these results may be used in lieu of the screening abdominal B-US.

Laboratory tests may be repeated, if required, due to operational reasons (e.g., insufficient specimen, coagulated sample, lost specimen, etc.).

All data will be reported on the relevant CRF page.

Age and HBV DNA level will be used for patient stratification at baseline.

### **6.3 Treatment exposure and compliance**

The investigator should promote compliance by instructing the patient to take the study drug exactly as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient should be instructed to contact the investigator if he/she is unable for any reason to take the study drug as prescribed.

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 pill count method is based on the number of pills returned by the patient at the succeeding visit minus the total number of pills received by the patient. The volume count method is based on the volume remaining in the bottle at the succeeding visit minus the volume total of telbivudine or placebo received by the patient.

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  $\geq 90\% - \leq 100\%$
- Fair compliance equals  $\geq 70\% - \leq 89\%$
- Poor compliance equals  $< 70\%$

If the compliance is  $< 90\%$ , the investigator needs to educate the patient to improve compliance. If the patient compliance does not improve, the investigator could consider discontinuing the patient from the study on the basis of the length of time and the number of pills or volume solution missed.

### **6.4 Efficacy**

Efficacy assessments will be evaluated by central laboratory as described in [Table 6-1](#). Key assessments are:

- Serum HBV DNA
- HBV Serologic Markers: HBsAg/Ab and HBeAg/Ab
- ALT
- Genotypic resistance

#### **6.4.1 Serum HBV DNA**

Serum HBV DNA is the best viral marker for the management of HBV disease. Serum HBV DNA level generally stands for the replication level of HBV in the patients and it is an indicator of disease prognosis. Several studies have shown that increasing HBV DNA level, starting at  $10^4$  copies/mL, is a predictor of risk for the development of cirrhosis and hepatocellular carcinoma, regardless of [REDACTED] baseline serum ALT level. Importantly, the suppression of HBV DNA level is correlated with higher rates of histologic response and lower rates of complications of liver disease.

HBV DNA analyses will be performed at a central reference laboratory through use of the COBAS TaqMan® HBV Test (Roche Molecular Systems, Branchburg, NJ, USA). Details of samples handling and methodology (including level of LLOQ and LOD) will be specified in the lab manual.

Serum samples for HBV DNA will be obtained at the defined visits in [Table 6-1](#). [REDACTED]

#### **6.4.2 HBV serological markers**

HBV Serologic Markers include HBsAg/Ab, HBeAg/Ab and Anti-HBc.

Hepatitis B surface antigen (HBsAg) clearance is the ultimate goal of therapy in patients with CHB. Emerging evidence has shown that on-treatment HBsAg levels may be a useful marker of antiviral efficacy and predictive of outcomes for pegylated interferon alfa-2a in patients with CHB. Current data on HBsAg kinetics during long-term treatment with oral antiviral treatment is limited. Emerging evidence suggests that rapid on-treatment HBsAg decline might be predictive of future HBsAg clearance in HBeAg negative patients treated with telbivudine ([Wursthorn et al 2010](#)).

Qualitative HBsAg/Ab, HBeAg/Ab will be assessed at the central laboratory using standard commercially available enzyme immunoassays.

Serum for HBsAg/Ab, HBeAg/Ab and Anti-HBc will be obtained according to the schedule in [Table 6-1](#).

HBsAb will only be measured for patients with undetectable HBsAg.

#### **6.4.3 Serum ALT**

Serum ALT normalization is an important clinically relevant efficacy endpoint. Elevated serum ALT levels are thought to reflect underlying hepatitis disease activity (i.e. active liver inflammation). Correspondingly, ALT normalization is an accepted therapeutic goal in hepatitis studies as it is thought to reflect a substantial reduction in hepatic disease activity.

ALT levels will be determined from serum samples obtained at all applicable study visits, via standard central laboratory testing.

#### **6.4.4 Genotypic Resistance surveillance**

Genotypic resistance will be assessed in real time in patients with virological breakthrough, in a central laboratory using serum storage samples, if available for VB at Weeks 24, 52, and 104. For VB confirmed at other times during the trial a specimen will be obtained from the patient to assess genotypic resistance. The genotypic sequencing results at the time of confirmed VB will be compared with the baseline results to assess treatment-emergent genotypic resistance and the cumulative rates of VB and/or genotypic resistance at Week 52 and 104 will be reported.

During the study, patients with confirmed VB and/or resistance will be discontinued from the clinical study.

Genotypic resistance will also be assessed in patients with HBV DNA  $\geq$ 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). Genotypic sequencing will be performed on stored serum samples from study visit at Week 24 and sequencing results will be compared with baseline sample assessment. Cumulative treatment-emergent genotypic resistance rates will be reported.

#### **6.4.5 Appropriateness of efficacy assessments**

The measurements of HBV DNA, HBV serological markers, ALT, and resistance surveillance are standard for CHB as evidenced by international CHB treatment guidelines ([Jonas et al 2010](#)). [REDACTED]

[REDACTED]

In case of insufficient serum volume taken at a certain visit to perform the required assessments as indicated in [Table 6-1](#), HBV DNA and biochemistry tests (including ALT and CK) should be measured as a priority.

### **6.5 Safety**

Key safety endpoints:

- Proportion of patients that discontinue study drug or require dose interruption due to treatment-emergent AEs
- Proportion of patients who develop SAEs
- Proportion of patients who develop Grade 3-4 AEs and AEs related to study drug (and if study drug temporarily interrupted)
- Proportion of patients who develop AESI (muscle related events)
- Other classical adverse events related to anti-HBV nucleos(t)ides analogues (including peripheral neuropathy, ALT flare, lactic acidosis, acute pancreatitis and hypersensitivity reactions)
- Proportion of patients with hepatic decompensation or HCC



- Proportion of patients who develop Grade 3-4 chemistry abnormality (including CK, ALT, AST, ALP, TB, PT, serum creatinine, serum cystatin C, serum phosphate, blood glucose), urinalysis abnormality and Grade 3-4 hematology abnormalities

Other safety assessments include physical exams (including growth (including Body weight, Body height and BMI) and development (Tanner Score)), vital signs and pregnancy monitoring.

#### **6.5.1 Physical examination**

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, and extremities, vascular and neurological. Complete physical examination is required at Baseline, Week 24, Week 52 and Week 104 (see [Table 6-1](#)).

Assessment of sexual maturation in males and females patients (for age group 2 and 3 at baseline visit) using Tanner staging ([Appendix 2](#)) should be performed at the following study visit: Baseline (visit 2), Week 24, Week 52 and Week 104.

Information for all physical examinations must be included in the source documentation at the study site. Information on sexual maturation assessment should be recorded on the specific Assessment of sexual maturation using Tanner Staging CRF page.

Significant findings that are present prior to the Inform consent signature must be included in the Relevant Medical History/Current Medical Conditions screen on the patient's CRF. Significant findings made after signing the inform consent form which meet the definition of an Adverse Event must be recorded on the Adverse Event screen of the patient's CRF.

#### **6.5.2 Vital signs**

The investigator will assess vital signs (heart rate, blood pressure, temperature and respirations) at each visit as indicated in [Table 6-1](#) and at the Early Treatment Discontinuation visit, or as necessary in case of AEs or under patient request.

Vital signs include BP and pulse measurement. After the patient has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured three times using an automated validated device, e.g. OMRON with an appropriately sized cuff. The repeat sitting measurements will be made at 1-2min intervals and the mean of the three measurements will be used. In case the cuff sizes available are not large enough for the patient's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.

#### **6.5.3 Height and weight**

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured at each visit as defined in [Table 6-1](#).

#### **6.5.4 Laboratory evaluations**

All specimens collected will be sent to the central lab. Details on the collections, shipment of samples, normal ranges and standard units for laboratory values and reporting of results by the central laboratory, are provided to investigators in the laboratory manual.



Additional blood will be collected as defined in [Table 6-1](#) for re-testing and storage purposes (i.e. genotypic sequencing). No genetic testing on patients' DNA will be performed.

The sample will be destroyed if no further testing is necessary.

Clinically notable laboratory findings are defined in [Appendix 1](#).

#### **6.5.4.1 Hematology**

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelet count will be measured. Blood samples for hematology will be collected at screening and selected visits as defined in the schedule of assessment [Table 6-1](#).

#### **6.5.4.2 Clinical chemistry**

Serum will be collected for the following to be measured: ALT, AST, alkaline phosphatase (ALP), total bilirubin (TB), albumin, blood glucose, creatinine, cystatin C, serum phosphate, CK, serum amylase and lipase. The Serum samples will be collected as defined in [Table 6-1](#).

The estimated glomerular filtration rate will be assessed by central lab using abbreviated Schwartz formula.

Plasma will be collected for Prothrombin time (PT and INR) at selected visits as shown in [Table 6-1](#).

#### **6.5.4.3 Urinalysis**

Urine pregnancy test and dipstick measurements for specific gravity, pH, protein, glucose and blood will be performed. Any confirmed abnormalities of urine test will be managed according to guidelines and clinical practice. A positive urine pregnancy test requires serum B-HCG to be performed.

Samples for urinalysis will be collected as defined in [Table 6-1](#).

#### **6.5.5 Liver ultrasound**

According to EASL 2013 guidelines ([Sokal et al 2013](#)), for HCC surveillance, liver ultrasound should be performed every 6 to 12 months depending on the stage of fibrosis.

In the study, patients will be followed with liver ultrasound every 6 months as indicated in [Table 6-1](#).

#### **6.5.6 Electrocardiogram (ECG)**

Not applicable.

#### **6.5.7 Pregnancy and assessments of fertility**

Female adolescent patient must have a serum pregnancy test administered to rule out pregnancy at screening and a urine pregnancy test at scheduled time points throughout the study, at end of the study and at the discretion of the investigator.

A positive urine pregnancy test requires immediate interruption of study drug until serum B-HCG is performed and found to be negative. If positive, the patient must be discontinued from

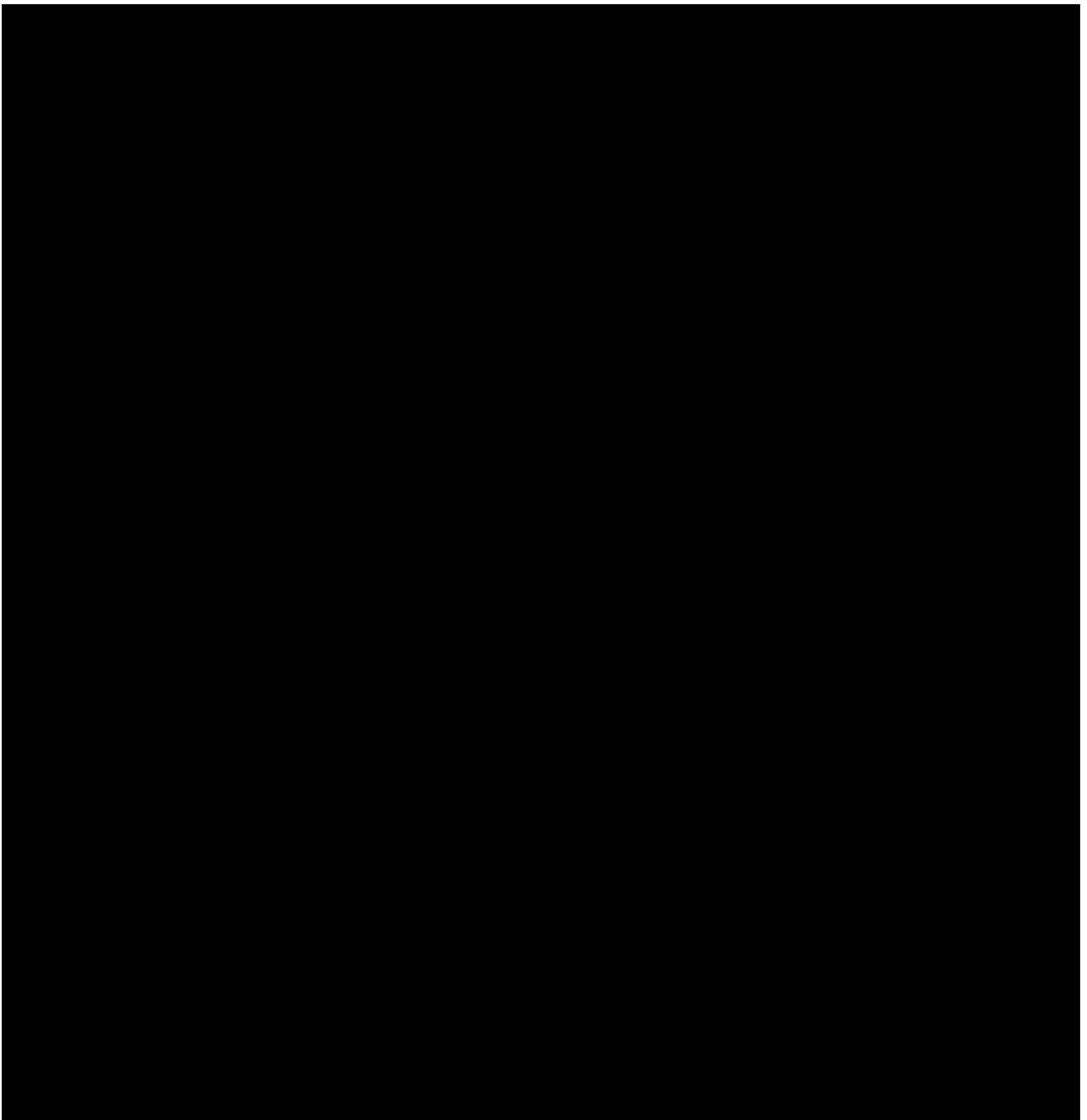
the trial and appropriate end of treatment procedure should be carried out. Such a pregnancy needs to be followed up by the investigator for safety analysis and reporting purposes.

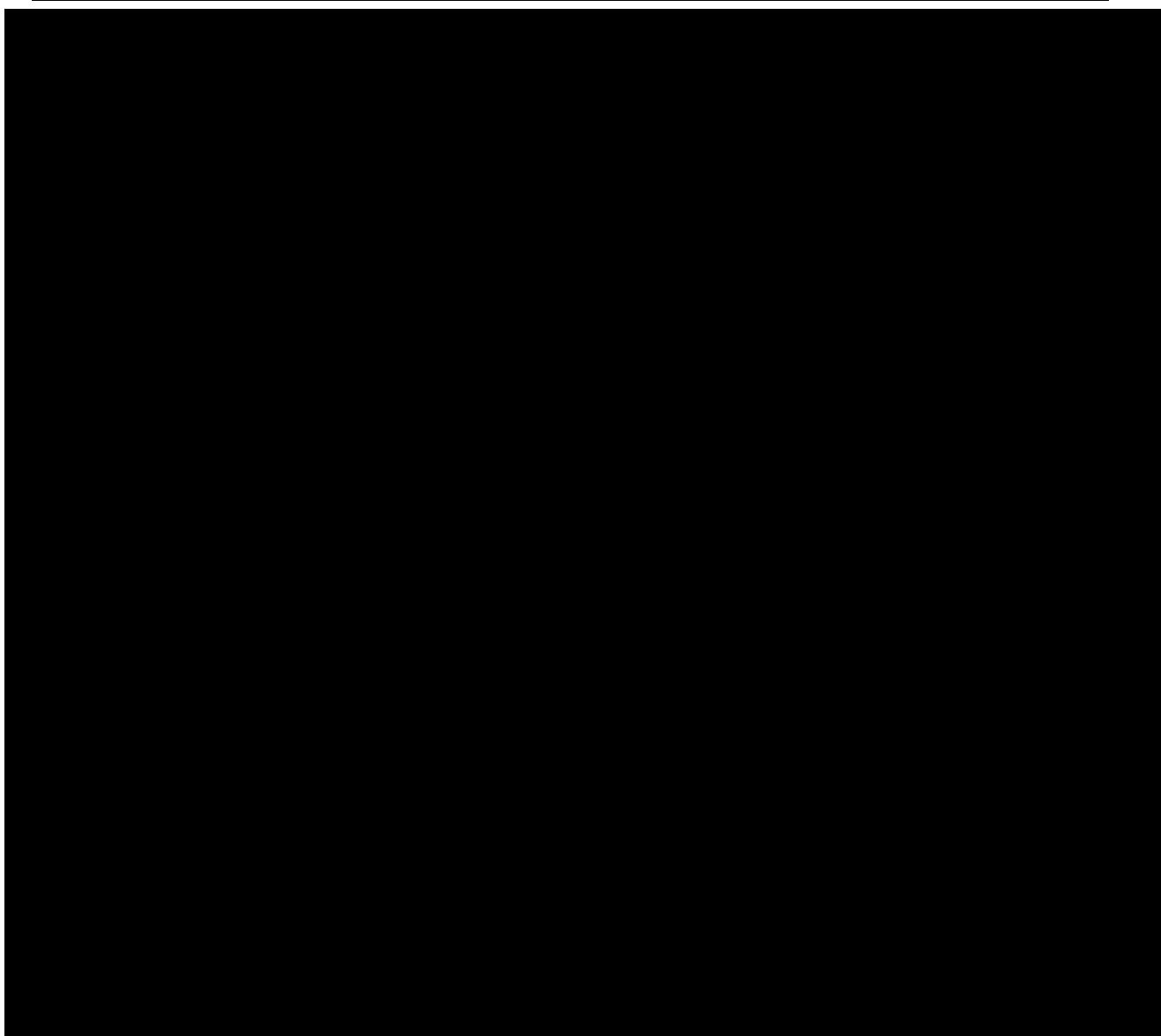
Data collection: see [Section 7.5](#) for details on reporting pregnancy.

All pregnancy cases need to be unblinded for safety management purposes. The unblinded information need to be communicated to the investigator on a case by case basis so that the patient can be informed.

#### **6.5.8      Appropriateness of safety measurements**

The safety assessments selected are standard for this indication/patient population.





## **7 Safety monitoring**

### **7.1 Adverse events**

An adverse event (AE) is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments.



Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patient with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying adverse events. Alert ranges for labs and other test abnormalities are included in [Appendix 1](#).

All adverse events must be recorded on the Adverse Events CRF page with the following information:

1. The severity grade (DMID AE grade)
  - Mild (Grade 1): usually transient in nature and generally not interfering with normal activities
  - Moderate (Grade 2): sufficiently discomforting to interfere with normal activities
  - Severe (Grade 3): prevents normal activities
  - Life-threatening (Grade 4)
2. Its relationship to the study drug(s) (suspected/not suspected)
3. Its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved should be reported.
4. Whether it constitutes a serious adverse event (SAE)
5. Action taken regarding the study drug

All adverse events should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e. further observation only); study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication given; non-drug therapy given; patient hospitalized/patient's hospitalization prolonged; its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown).

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB) or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.



The investigator should also instruct each patient to report any new adverse event (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. This information should be recorded in the investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

## 7.2 Serious adverse events

### 7.2.1 Definition of SAE

An SAE is defined as any adverse event (appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical conditions(s) which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe (see Annex IV, ICH-E2D Guideline).

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (see Annex IV, ICH-E2D Guideline).



All AEs (serious and non-serious) are captured on the CRF, SAEs also require individual reporting to local Novartis Drug Safety and Epidemiology Department as per [Section 7.2.2](#).

### **7.2.2 Serious adverse event reporting**

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days after the last study visit must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after the 30 days period (after the last study visit) should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs (either initial or follow-up information) is collected and recorded on the paper Serious Adverse Event Report Form. The investigator must assess the relationship of any SAE to study drug, complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours after awareness of the SAE to the local Novartis Drug Safety and Epidemiology Department. The telephone and fax number of the contact persons in the local department of Drug Safety and Epidemiology, specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow-up information should be provided using a new paper SAE Report Form stating that this is a follow-up to a previously reported SAE

Follow-up information provided should describe whether the event has resolved or continues, if and how it was treated, whether the treatment code was broken or not and whether the patient continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the investigational treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same investigational treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

### **7.3 Liver safety monitoring**

Telbivudine is an antiviral nucleoside analogue with inhibitory effects on HBV DNA and an indication in compensated CHB. No liver toxicity has been reported with telbivudine from

preclinical studies and based on 9,715 subjects/patients exposure in clinical trials and 329,556 PTY (Patient Treatment Years) post-marketing database (as of 31-Aug-2012). No liver toxicity was confirmed in another internal post marketing surveillance with a total exposure of 392,452 PTY (as of 28-Feb-2013).

The main liver events (ALT flare/ flare) reported from Telbivudine treated patients are due to effects of treatment failure (associated with suboptimal antiviral effect - HBV DNA increase and / or VB). Some of these situations could be prevented by monitoring HBV DNA at each visit ([EASL 2012](#)).

Another potential reason of ALT increase / flare under CHB treatment could be associated with a positive antiviral treatment response, i.e., HBeAg seroconversion ([EASL 2012](#)).

In the current protocol, the assessment schedule will adequately monitor liver events and has been used as current standards for CHB trials.

- Standard serum blood chemistry tests for monitoring hepatotoxicity (ALT, AST, ALP, total bilirubin) are performed at each scheduled visit every 4-12 wks.
- Any patients with ALT flare (defined as ALT elevation  $> 10 \times \text{ULN}$  and  $> 2 \times$  baseline, per AASLD guideline); or ALT  $> 3 \times \text{ULN}$  &  $> 2 \times$  baseline AND (TBil  $> 2 \times \text{ULN}$  or INR  $> 1.5$ ) or with hepatic decompensation will be discontinued from the study (see [Section 5.5.9](#)).
- Exclusion criteria: ALT  $> 10 \times \text{ULN}$  or  $< 1.5 \times \text{ULN}$ . Patients with liver decompensation or other causes of liver diseases or total bilirubin  $\geq 2 \times \text{ULN}$  or INR  $> 1.5$  excluded.

## 7.4 Renal safety monitoring

Telbivudine is an antiviral nucleoside analogue with no known potential to cause Drug induced nephrotoxicity (no adverse preclinical in vitro or in vivo renal safety signal, mode of action well characterized with no known nephrotoxicity (no renal safety findings)).

Renal events in the pediatric population should be defined as 25% decrease in eGFR ([Akcan-Arikan et al 2007](#)) using age-specific normal values for eGFR and serum/urinary normal values ([Appendix 1](#)).

Serum and urine samples are collected as defined in [Table 6-1](#) for the measures of creatinine, cystatin C, serum phosphate, urine analysis for specific gravity, pH, protein, and blood.

Any confirmed abnormalities of urine test should be managed according to guidelines and clinical practice.

To estimate the glomerular filtration rate, the abbreviated Schwartz formula ([Schwartz 2009](#)) based on length (L= height (cm)) and serum creatinine (Scr) should be used in the pediatric population:

eGFR =  $0.413 \times (\text{height}/\text{serum creatinine})$  (height in cm; serum creatinine in mg/dl).

## 7.5 Pregnancy reporting

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination,

details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Pregnancies that are noted prior to administration of study medication but after the informed consent process may be considered to be reported at the discretion of the investigator especially where causality is suspected.

Pregnancy should be recorded on a Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

**Pregnancy Registry:** to monitor fetal outcomes of pregnant women exposed to telbivudine, investigators are encouraged to register such patients in the Antiretroviral Pregnancy Registry.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study during the perinatal or neonatal (first 28 days of life for a newborn child) periods. Consent to report information regarding these pregnancy outcomes should be obtained from the female partner.

## **7.6 Prospective suicidality assessment**

Not applicable.

## **7.7 Adverse events of special interest (AESI) reporting**

For the purpose of this study, the diagnosis and reporting of adverse events of special interest (AESI) defined as muscle related events (including myopathy and other types of muscle events) will follow specific guidance as described in this section. All AESIs' should be reported on AE CRF page and SAE (if applicable). All other known classic adverse events under telbivudine treatment will be monitored and reported in this study following the normal AE process.

Patients with complaints or observation by parents of new or worsening muscle weakness, OR with new or worsening muscle pain (myalgia), OR patients with complaints or observation by parents of change in the urine color (e.g., dark urine) should be managed according to the algorithm provided in [Appendix 3](#).

All patients being followed with this algorithm should have muscle strength tested ([Appendix 5](#)), Muscle Symptom Questionnaire ([Appendix 4](#)) administered, and serum CK checked at initial and follow up visits following the muscle management algorithm. More detailed neurological evaluation, EMG or muscle biopsy will not be routinely recommended for the diagnosis of myopathy in this pediatric study; and the need of conducting these procedures will be decided at the discretion of the investigators.

### **Muscle Strength Testing**

Each of the muscle groups tested in the arms and legs will be graded on the Medical Research Council (MRC) grading system (0 to 5) ([Appendix 5](#)). The muscle strength testing exam

should be performed for all patients ( $\geq 6$  years) with muscle related events as described in the muscle management algorithm. If the muscle strength testing exam can't be performed (patients too young or physical examination not feasible), a subjective evaluation will be assessed using Muscle Symptom Questionnaire ([Appendix 4](#)).

### **Muscle Symptom Questionnaire**

The Muscle Symptom Questionnaire includes subjective assessments of muscle strength of legs (Question A), arms (Question B), and muscle pains (myalgia) (Question C) ([Appendix 4](#)). This questionnaire must be administered to all patients with complaints or observation by parents of new or worsening muscle weakness, OR new or worsening muscle pain (myalgia), OR patients' complaints or observation by parents of change of urine color (e.g dark urine). The data collected from the questionnaire will be recorded in the study CRF.

### **Discontinuation criteria defined in the algorithm**

There are 3 situations defined in the algorithm

- Situation A: MRC score  $< 58$  or  $\geq 1$  drop in MRC in 2 or more muscle groups OR 2 or more situations with  $\geq$  Grade 2 in arms or legs as defined in muscle questionnaire (if  $< 6$  years or if strength tests not measurable)
- Situation B: Muscle pain score  $> 5$  OR myalgia affect functions (2 or more situations with  $\geq$  Grade 2 in arms or legs as defined in muscle questionnaire)
- Situation C: CK elevation  $\geq 7 \times$  ULN

The study drug should be discontinued if meeting either one of below discontinuation criteria:

- If all 3 situations (A, B, C) occur at the same visit independently of degree / score / value, study drug should be discontinued at the current visit.
- If 2 out of the 3 situations (A, B, C) occur at one visit, study drug should be discontinued at the current visit.
- If 1 of 3 situations (A, B, C) occurs at one visit, patients should be followed after 2 visits, if there is no improvement / is worsening in 2 weeks, study drug should be discontinued.
- In addition, if the patient is diagnosed with rhabdomyolysis (defined as CK  $> 50 \times$  ULN (or 10,000 IU/L ([Joy et al 2009](#))) with organ damage, usually renal compromise), the drug should be discontinued.

### **Definition of myopathy**

The definition of myopathy is based on the definition recommended by NLA (National Lipid Association) for statins ([McKenney et al 2006](#)). In this protocol, patients with symptoms of myalgia (muscle pain, soreness, or cramps), weakness, AND creatine kinase  $\geq 10 \times$  ULN will be assessed for the diagnosis as myopathy.

### **Reporting of AESIs**

All AESI's should be recorded on the AE CRF pages. For muscle related AESIs, specific CRF pages should be filled and the muscle related AESI Report Form must be sent via FAX

to the Novartis Global Medical Specialist. The telephone and fax number of the contact persons will be listed on the AESI document. The original copy of the muscle related AESI Report Form (initial and follow up) and the fax confirmation sheet must be kept with the source documentation at the study site.

Follow-up information should be sent to the same person to whom the original AESI Report Form was sent, using a new AESI Report form stating that it is a follow-up to the previously reported AESI and giving the date of the original report. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or withdrew from study participation.

## **8 Data review and database management**

### **8.1 Site monitoring**

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis or CRO representative will review the protocol and CRFs with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

If needed, continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

### **8.2 Data collection**

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms using fully validated software that conforms to 21 CFR Part 11



requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to the CRO working on behalf of Novartis. The Investigator must certify that the data entered into the Electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

### **8.3 Database management and quality control**

CRO staff working on behalf of Novartis review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Novartis staff that will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Concomitant procedures, non-drug therapies and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Randomization codes and data about all study drug(s) dispensed to the patient and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis (or a designated CRO).

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked. Any changes to the database after that time can only be made after written agreement by Novartis Development management.

### **8.4 Data Monitoring Committee**

An independent Data Monitoring Committee composed of clinicians experienced in clinical care and/or clinical research in CHB pediatric population and a statistician, will perform regular safety data review and where appropriate, to request and review additional safety and/or efficacy analyses during the course of the trial. A separate charter will be prepared to define the scope of the DMC (e.g. data to be reviewed, access to reports, actions on the study conduct, frequency and method of data transfers, format/timing of reports).



## 8.5 Adjudication Committee

Not required.

# 9 Data analysis

The primary analysis will be done at Week 24. Additional analyses will be done at Week 52 (intended for submissions to Health Authorities) and Week 104 (final analysis).

## 9.1 Analysis sets

The following analysis sets will be used in this trial:

**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).

**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.

**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.

**Per-protocol set (PPS):** The PPS will be defined as a subset of FAS who do not have major protocol deviations, such as patient has poor compliance or patient takes prohibited medications during treatment period. Other criteria for major protocol deviations will be established and documented based upon the review of data before clinical database lock for the Week 24 primary data analysis.

**Modified Full analysis set (mFAS):** The mFAS (a subset of FAS) will be used for selected efficacy and safety analyses beyond Week 24. The set will be defined only for telbivudine randomized group. Criteria for inclusion in this set will be detailed in the statistical analysis plan (RAP), to be finalized before clinical database lock for the Week 24 primary data analysis.

Patients will be kept in the same age group from baseline for data analysis during the whole study period.

## 9.2 Patient demographics and other baseline characteristics

Descriptive statistics of demographics and baseline characteristics will be provided for overall [REDACTED] populations.

### **9.3 Treatments**

The numbers of patients who receive each treatment and the duration of exposure will be summarized for the Safety set. In calculation of duration, periods of temporary interruption of study medication for safety reasons will be included. Further, frequency of dose change (including temporary dose interruption) by reasons will be presented.

Prior and concomitant therapies will be listed. The frequency and percentage of patients who used prior or concomitant medication will be summarized by preferred term (WHO Drug) and treatment arm. Concomitant medications will also be checked for protocol deviations. Patients who took prohibited concomitant medications will be noted in the summary of protocol deviations.

The Investigator will assess the patient's compliance for each visit during treatment. Patients' compliance will be summarized by visit.

### **9.4 Analysis of the primary variable**

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. The analysis of primary efficacy variable, as well as all other analyses, will be done for overall [REDACTED] patient population.

[REDACTED]

The primary variable will be summarized by treatment groups (arms). Comparisons will be made between the telbivudine arm and the placebo arm for the overall population. The same analysis will be done by age groups, except in the younger group (from 2 to less than 6 years old) where the number of patients enrolled is anticipated to be small.

[REDACTED]

Descriptive statistics will be provided for all endpoints.

#### **9.4.1 Variable(s)**

The primary efficacy variable is the proportion of patients achieving HBV DNA <300 copies/mL (51 IU/mL) at Week 24.

#### **9.4.2 Statistical model, hypothesis, and method of analysis**

For the primary analysis, the null hypothesis ( $H_0$ ) is that the proportion of patients in the overall population achieving HBV DNA <300 copies/mL (51 IU/mL) in the telbivudine arm is not different from that of placebo arm. The alternative hypothesis ( $H_1$ ) is the proportion of patients in the overall population achieving HBV DNA <300 copies/mL (51 IU/mL) between the two groups is not the same. That is:

$$H_0: \pi_1 = \pi_2 \text{ vs.}$$

$$H_1: \pi_1 \neq \pi_2$$



Where,  $\pi_1$  and  $\pi_2$  are the proportion of HBV DNA  $<300$  copies/mL (51 IU/mL) patients in the telbivudine and placebo arms, respectively.

The hypothesis will be tested using Fisher Exact test method. The two sided test will be done at a significance level of 5% (Type I error,  $\alpha = 0.05$ ).

Two sided 95% exact confidence interval will be provided for the difference of proportions of the two groups.

#### **9.4.3 Handling of missing values/censoring/discontinuations**

Missing HBV DNA value at Week 24 will be imputed with the closest HBV DNA value to Week 24 (either before or after Week 24) for primary endpoint (HBV DNA  $< 300$  copies/mL (51 IU/mL)). In case of equal distances from Week 24, the measurement before week 24 will be used.

Patients who discontinue the treatment due to satisfied efficacy as described in [Section 5.5.9](#) (complete response defined by HBV DNA  $< 300$  copies/mL (51 IU/mL), ALT normalization and HBeAg seroconversion) will be treated as responders.

#### **9.4.4 Supportive analyses**

To check the robustness of the primary analysis as described in [Section 9.4.2](#), two sets of supportive analyses will be performed: (1) analysis on Per Protocol set and (2) Age 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.

### **9.5 Analysis of secondary variables**

#### **9.5.1 Efficacy variables**

The secondary efficacy variables (corresponding to the secondary objectives in [Section 2.2](#)) will be summarized by treatment groups (arms).

For Week 24 treatment comparison, where applicable:

- (1) Dichotomous variables will be analyzed with Fisher's Exact Test, similar to primary efficacy analysis,
- (2) Continuous variables will be analyzed with Analysis of Covariance (ANCOVA) model, including treatment, stratification factors, country/region and baseline values as co-factors.

Time to event variables will be analyzed using survival analysis (Kaplan-Meier estimates).

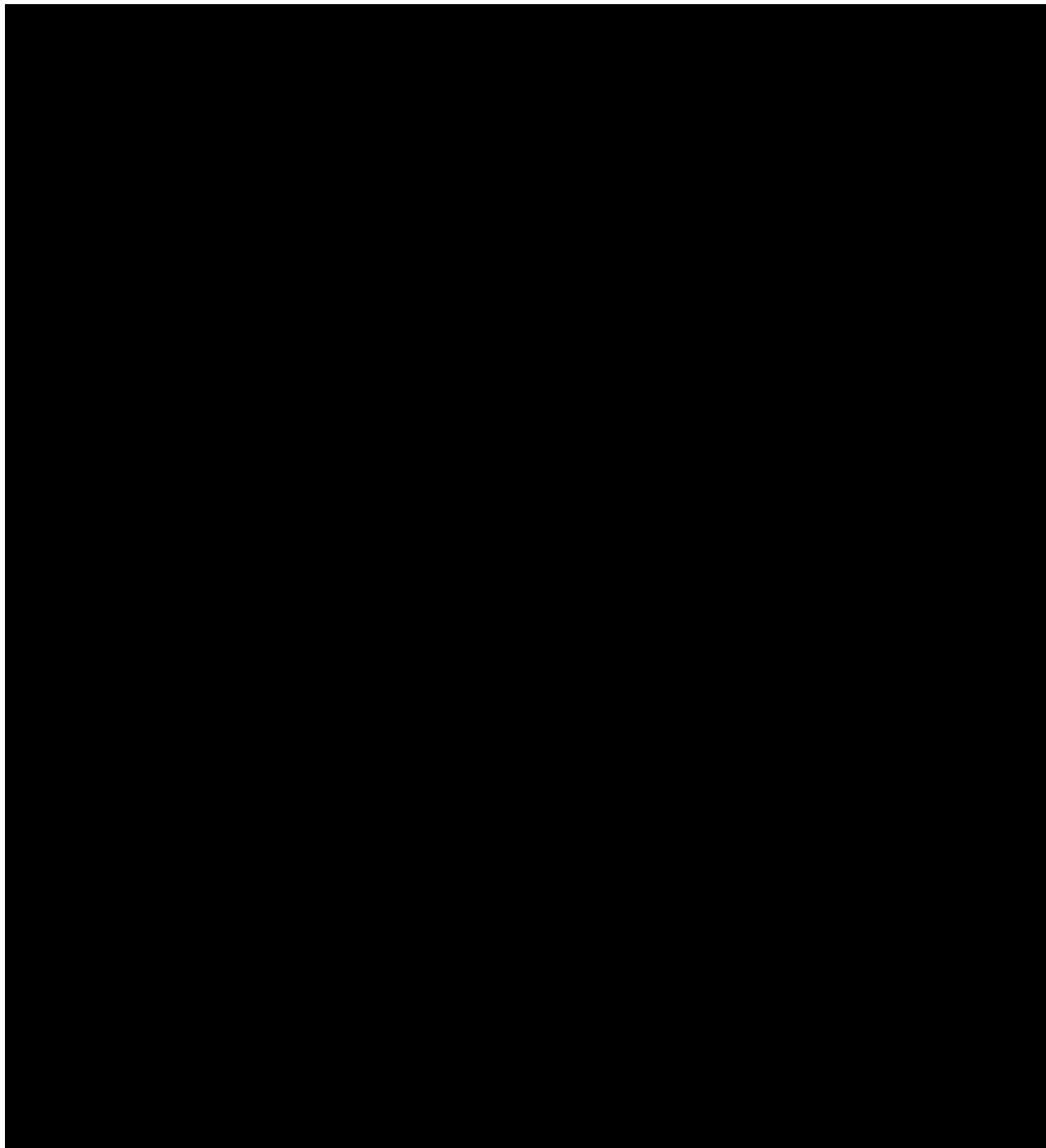
#### **9.5.2 Safety variables**

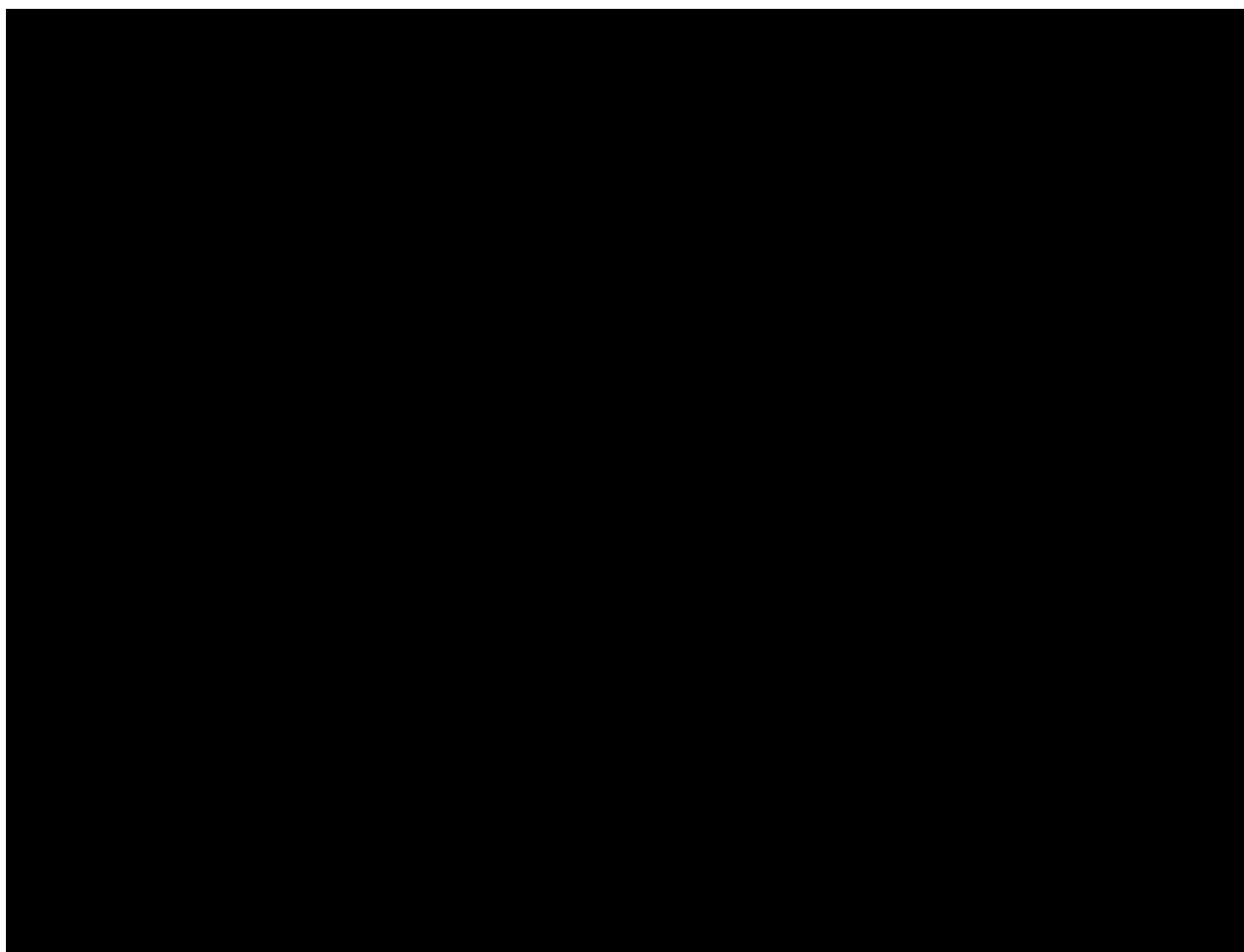
The safety analyses will include SAEs, AEs (all grades, AEs related to study drug, leading to study drug discontinuation or dose interruption), AESI (including muscle related events, Grade 3-4 CK elevations, as well as other compound class-related AESI ([Section 3.6](#))), laboratory values (hematology and chemistry), development of liver decompensation and/or

HCC, physical exams (including growth (including Body weight, Body height and BMI) and development (Tanner Score), as well as abdominal B-US) and vital signs. All safety data will be summarized by treatment group; the placebo randomized patients will be included in the safety analysis set.

To estimate the glomerular filtration rate, the abbreviated Schwartz formula ([Schwartz 2009](#)) based on length (L= height (cm)) and serum creatinine (Scr), will be used:

eGFR =  $0.413 \times (\text{height}/\text{serum creatinine})$  (height in cm; serum creatinine in mg/dl).





## **9.6      Interim analyses**

Interim analyses are planned for weeks 24 (primary analysis) and 52.

## **9.7      Planned analyses**

Data will be analyzed at three time points:

1.      The primary analysis will be at Week 24; a comparison between treatment groups will be carried out only at the Week 24 analysis.
2.      An additional analysis will be performed when all patients complete Week 52, and a 52 week report will be prepared for that analysis.
3.      The final analysis will be performed at the end of study, which includes a 12-weeks follow-up period following Week 104 treatment completion. The end of study analysis is the final analysis.

A DMC is planned to conduct regular safety analyses for patient monitoring and where appropriate, to request and review additional safety and/or efficacy analyses (See [Section 8.4](#) for details).



## **9.8 Sample size calculation**

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<sub>10</sub> for HBeAg positive patients. In this study, 80% of patients with baseline HBV DNA < 9 log<sub>10</sub> 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) will provide > 99% power to test the primary hypothesis ([Section 9.4.2](#)), at 5% significance level (Type I error,  $\alpha$ ), for overall patients population.

## **10 Ethical considerations**

### **10.1 Regulatory and ethical compliance**

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

### **10.2 Informed consent procedures**

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.



Women of child bearing potential should be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

### **10.3 Responsibilities of the investigator and IRB/IEC**

Before initiating a trial, the investigator/institution should obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to patients.

Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

### **10.4 Publication of study protocol and results**

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

## **11 Protocol adherence**

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of patients should be administered as deemed necessary on a case by case basis. Under no circumstances should an investigator collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

### **11.1 Protocol Amendments**

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC prior to implementation. Only amendments that are intended to eliminate an apparent immediate hazard to patients may be implemented immediately provided the Health Authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.



Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in **Section 7** (Safety Monitoring) should be followed.

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Available upon request

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### **Internal references**

Investigator Brochure v 15

Core data Sheet, version 1.0 (dated: 7-May-2014)

## 13 Appendix 1: Clinically notable laboratory values and vital signs

**Table 13-1 Clinically notable laboratory values and vital signs**

	GRADE 1 (Mild)	GRADE 2 (Moderate)	GRADE 3 (Severe)	GRADE 4 (Potential Life-threatening)
<b>Hematology</b>				
Hemoglobin for children greater than 2 years of age	10-10.9 mg/dL	7.0-9.9 mg/dL	<7.0 mg/dL	Cardiac Failure secondary to anemia
Absolute Neutrophil Count	750-1200/mm <sup>3</sup>	400-749/mm <sup>3</sup>	250-399/mm <sup>3</sup>	<250/mm <sup>3</sup>
Platelets	-----	50,000-75,000/mm <sup>3</sup>	25,000-49,999/mm <sup>3</sup>	<25,000/mm <sup>3</sup>
Prothrombin Time (PT)	1.1-1.2 x ULN	1.3 -1.5 x ULN	1.6 -3.0 x ULN	>3.0 x ULN
Partial Thromboplastin Time (PTT)	1.1-1.6 x ULN	1.7-2.3 x ULN	2.4 -3.0 x ULN	>3.0 x ULN
<b>Gastrointestinal</b>				
Bilirubin (when accompanied by any increase in other liver function test)	1.1 - <1.25 x ULN	1.25 - <1.5 x ULN	1.5 – 1.75 x ULN	> 1.75 x ULN
Bilirubin (when other liver function are in the normal range)	1.1 - <1.5 x ULN	1.5 - <2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
AST (SGOT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
ALT (SGPT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN

GGT	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Pancreatic Amylase	1.1-1.4 x ULN	1.5-1.9 x ULN	2.0-3.0 x ULN	>3.0 x ULN
Uric Acid	7.5-9.9mg/dL	10-12.4 mg/dL	12.5-15.0 mg/dL	>15.0 mg/dL
Creatine Phosphokinase	>1.0 – 3.0 x ULN	>3.0 – 7.0 x ULN	>7.0 – 10.0 x ULN	>10 x ULN
<b>Electrolytes</b>				
Creatinine				
2 Years- 12 Years of age	0.7-1.0 x ULN	1.1-1.6 x ULN	1.7-2.0 x ULN	>2.0 x ULN
Greater than 12 Years of age	1.0-1.7 x ULN	1.8-2.4 x ULN	2.5-3.5 x ULN	>3.5 x ULN
Hypernatremia		<145-149 mEq/L	150-155 mEq/L	>155 mEq/L or abnormal sodium AND mental status changes
Hyponatremia		130-135 mEq/L	129-124 mEq/L	<124 mEq/L or abnormal sodium AND mental status changes
Hyperkalemia	5.0-5.9 mEq/L	6.0-6.4 mEq/L	6.5-7.0 mEq/L	>7.0 mEq/L or abnormal potassium AND cardiac arrhythmia
Hypokalemia	3.0-3-5 mEq/L	2.5-2.9 mEq/L	2.0-2.4 mEq/L	<2.0 mEq/L or abnormal potassium AND cardiac arrhythmia
Hypercalcemia	10.5-11.2mg/dL	11.3-11.9 mg/dL	12.0-12.9 mg/dL	>13.0 mg/dL
Hypocalcemia	7.8-8.4 mg/dL	7.0-7.7 mg/dL	6.0-6.9 mg/dL	<6.0 mg/dL

Hypomagnesemia	1.2-1.4 mEq/L	0.9-1.1 mEq/L	0.6-0.8 mEq/L	<0.6 mEq/L or abnormal magnesium AND cardiac arrhythmia
Hypoglycemia	55-65 mg/dL	40-54 mg/dL	30-39 mg/dL	<30 mg/dL or abnormal glucose AND mental status changes
Hyperglycemia	116-159 mg/dL	160-249 mg/dL	250-400 mg/dL	>400 mg/dL or ketoacidosis
Proteinuria	Tr-1+ or <150 mg/day	2+ or 150-499 mg/day	3+ or 500-1000 mg/day	4+ or Nephrotic syndrome >1000 mg/day
Hematuria	Microscopic <25 cells/hpf	Microscopic >25 cells/hpf		Gross hematuria
Glomerular filtration rate *				
eGFR values	60–89 ml/min/1.73m <sup>2</sup>	30–59 ml/min/1.73m <sup>2</sup>	15–29 ml/min/1.73m <sup>2</sup>	<15 ml/min/1.73m <sup>2</sup>
Description	Kidney damage with mild reduction of GFR	Moderate reduction of GFR	Severe reduction of GFR	Kidney failure

\* Adapted from National Kidney Foundation's Kidney Disease Outcomes Quality Initiative clinical practice guidelines for chronic kidney disease in children and adolescents: evaluation, classification, and stratification ([Hogg et al 2003](#))

## **14      Appendix 2: Assessment of sexual maturation in males and females under 18 years of age (Tanner staging)**

### **Male patients - Development of external genitalia**

- Stage 1: Pre-adolescent. Testes, scrotum, and penis are of about the same size and proportion as in early childhood.
- Stage 2: The scrotum and testes have enlarged and there is a change in the texture of the scrotal skin.
- Stage 3: Growth of the penis has occurred, at first mainly in length; these has been further growth of testes and scrotum
- Stage 4: Penis further enlarged in length and breadth with development of glans. Testes and scrotum further enlarged. There is also further darkening of the scrotal skin
- Stage 5: Genitalia adult in size and shape

### **Female patients - Breast development**

- Stage 1: Pre-adolescent; elevation of papilla only.
- Stage 2: Breast bud stage; elevation of breast and papilla as a small mound, enlargement of areola diameter.
- Stage 3: Further enlargement of breast and areola, with no separation of their contours.
- Stage 4: Projection of areola and papilla to form a secondary mound above the level of the breast.
- Stage 5: Mature stage; projection of papilla only, due to recession of the areola to the general contour of the breast.

The girls will be asked at each visit if they had begun to menstruate.

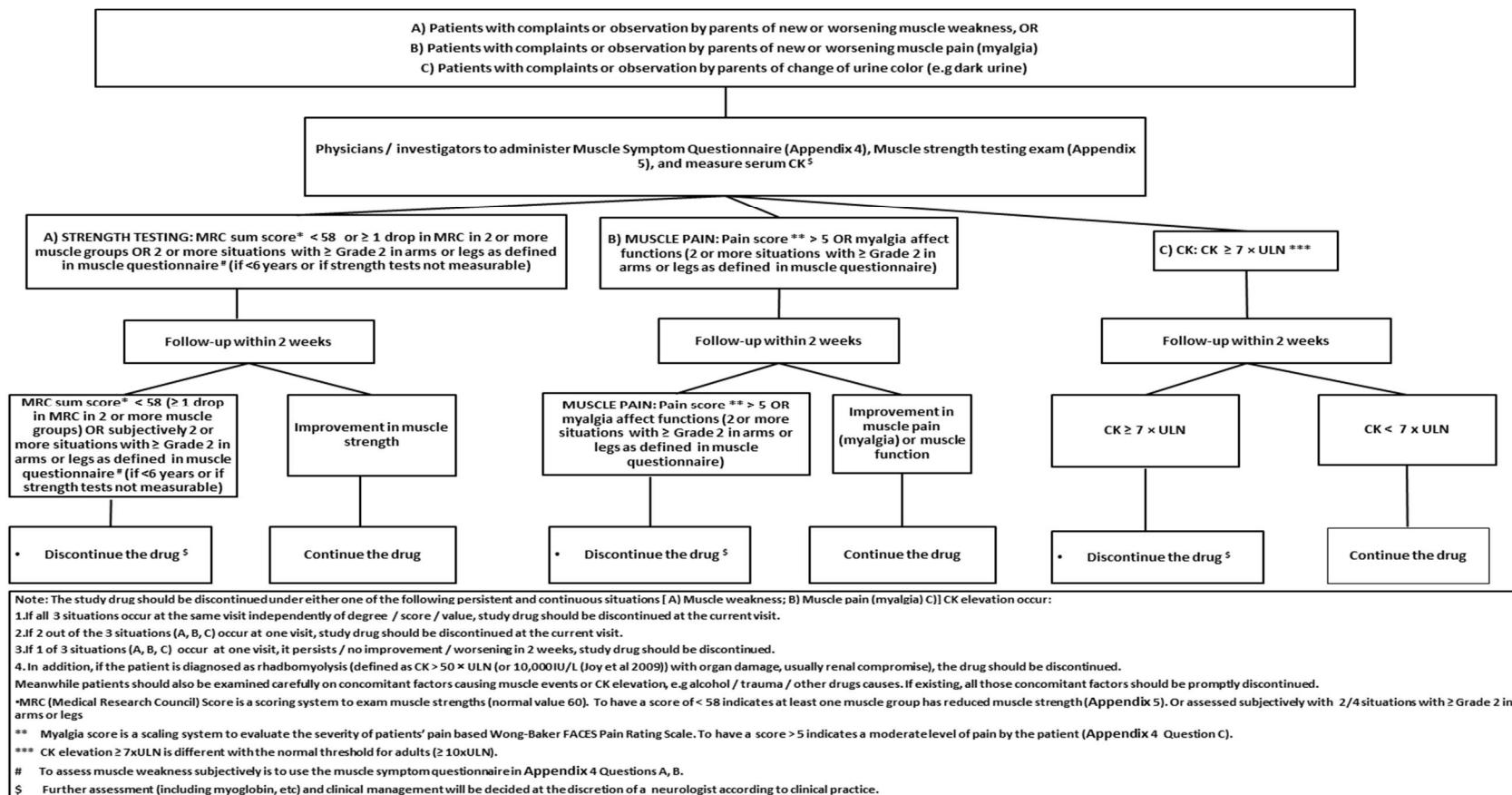
### **Male and female patients - Pubic hair**

- Stage 1: Pre-adolescent (can see velus hair similar to abdominal wall).
- Stage 2: Sparse growth of long, slightly pigmented, downy hair, straight or only slightly curled, appearing chiefly along the labia or the base of the penis.
- Stage 3: Considerably darker, coarser and more curled hair. The hair spreads sparsely over the junction of the pubes.
- Stage 4: Hair is now adult in type, but the area covered by is still considerably smaller than in most adults. There is no spread to the medial surface of thighs.
- Stage 5: Adult in quantity and type, distributed as an inverse triangle of the classically feminine pattern.

[Marshall and Tanner \(1970\)](#); [Marshall and Tanner \(1969\)](#)

## 15 Appendix 3: Muscle management algorithm

Figure 15-1 Muscle management algorithm



## 16 Appendix 4: Muscle symptom Questionnaire (initial and follow-up visits)

Questions to be raised by the investigators answered by patient or parents and transcribed by site staff in the eCRF.

**Table 16-1 Muscle Symptom Questionnaire (Initial and follow-up visits)**

<b>Question A: Assessment on Muscle Strength of Legs *</b>					
Have you experienced or as parents you noticed for your child, <i>new or worsening</i> <sup>#</sup> difficulty in either one of the following 4 situations? If yes, please provide a grade per the grading system below the table, and provide a time ( <i>dd-mmm-yy</i> ) when did you first notice this?					
1. Walking					
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Comments:					
2. Running					
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Comments:					
3. Climbing Steps					
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Comments:					
4. Rising from sitting positions					
<i>Have you experienced (or the parents noticed) any difficulty in standing from the sitting position? or if arising from the floor</i>					
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Comments:					

**\*Grading systems for the answer of the above questions A (1-4) for Legs**

0 = Normal

1 = Minor symptoms in one or both legs but not affecting the functions listed

2 = Moderate symptoms in one or both legs affecting but not preventing the function listed

3 = Severe symptoms in one or both legs preventing the functions listed

4 = Severe symptoms in both legs preventing the functions listed but some purposeful movement still possible

5 = Severe symptoms in both legs preventing purposeful movements

Note: If a child had an injury in one side of body and can't perform the muscle strength test on this particular side, the muscle strength score of the other body side needs to be evaluated and need be doubled as the scores of both sides.

**Comments:**

How long have you noticed muscle weakness in your legs?

< 3 days  3 - < 6 days  6 - < 9 days  9 - < 14 days  ≥ 14 days  NA

Adapted from [Merkies et al 2002](#).

**Question B: Assessment on Muscle Strength of Arms \*\***

Have you experienced or as parents you noticed for your child *new or worsening<sup>#</sup>* difficulty in either one of the following 4 situations? If yes, please provide a grade per the grading system below the table, and provide a time (*dd-mmm-yy*) when did you first notice this?

1. Reaching overhead e.g. brushing or combing hair

<input type="checkbox"/>					
Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5

Comments:

2. Reaching for things above the shoulders

<input type="checkbox"/>					
Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5

Comments:

3. Pulling or pushing objects, e.g. lifting a liter of milk

<input type="checkbox"/>					
Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5

Comments:

4. Throwing a ball					
<input type="checkbox"/>					
Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Comments:					

**\*\* Grading systems for the answer of the above questions A (1-4) for Arms**

0 = Normal

1 = Minor symptoms in one or both arms but not affecting the functions listed

2 = Moderate symptoms in one or both arms affecting but not preventing the functions listed

3 = Severe symptoms in one or both arms preventing the functions listed

4 = Severe symptoms in both arms preventing the functions listed but some purposeful movements still possible

5 = Severe symptoms in both arms preventing the purposeful movements

Note: If a child had an injury in one side of body and can't perform the muscle strength test on this particular side, the muscle strength score of the other body side needs to be evaluated and need be doubled as the scores of both sides.

**Comments:**

How long have you noticed muscle weakness in your arms?

< 3 days  3-6 days  6-9 days  9-14 days  ≥14 days  NA

Adapted from [Merkies et al 2002](#).

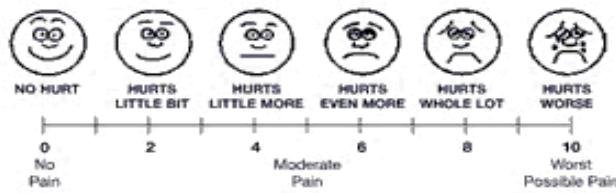
**Question C: Assessment on Muscle Pains (Myalgia)**

Have you experienced or as parents you noticed for your child any new or worsening muscle pain since starting study drug treatment for CHB in CLDT600A2306 study in one or more limbs at rest or after exercise? If yes, please provide a grade per the grading system in the lower part of the table, and provide a date (dd-mm-yy) when did you first notice this?

*Reference: Muscle pain scaling system – Wong-Baker FACES Pain Rating Scale*

### Wong-Baker FACES Pain Rating Scale

Intensity: (using scales below)



From Wong D.L., Hockenberry-Eaton M., Wilson D., Winkelstein M.L., Schwartz P.: Wong's Essentials of Pediatric Nursing, ed. 6, St. Louis, 2001, p. 1301. Copyrighted by Mosby, Inc.  
Reprinted by permission.

Please select a score for the muscle pain (myalgia):

<input type="checkbox"/>		<input type="checkbox"/>								
0		2		4		6		8		10

#### Comments:

Where is the muscle pain on your body? Legs  Arms   
Other locations  if ticked, please specify  
\_\_\_\_\_

Does it occur during rest or exercises? Rest  Exercises

How long have you noticed muscle pain (myalgia)?

< 3 days  3 - <6 days  6 - < 9 days  9 - < 14 days  ≥14 days  NA

Also please use the symptom questionnaire above to note if the pain is affecting any of the functions listed in the muscle symptom questionnaire above.

[Hockenberry and Wilson 2009](#), Used with permission. Copyright Mosby.

## 17 Appendix 5: Muscle strength testing exam

Table 17-1 Muscle Strength Testing Exam

*Neuromuscular Exam with Strength Testing - Medical Research Council (MRC) Score*

*Was a neuromuscular exam with strength testing performed? No  Yes\**

*\*If YES, please provide results.*

Location	Specify Muscle Group (Enter only one major muscle group per line)	Muscle strength score for left muscles (L)	Muscle strength score for right muscles (R)	Subtotal
Arm	Abduction of Arm			
	Flexion of the forearm			
	Extension of the wrist			
Leg	Flexion of the Hip			
	Extension of the Knee			
	Dorsal flexion of the foot			
<b>Total**</b>				
<i>Body Location</i>	<i>Strength Score</i>			
<i>A = Arm</i>	<i>0 = no contraction</i>			
<i>L = Leg</i>	<i>1 = muscle flicker, but no movement</i>			
	<i>2 = movement possible, but not against gravity (test the joint in its horizontal plane)</i>			
	<i>3 = movement possible against gravity, but not against resistance by the examiner</i>			
	<i>4 = movement possible against some resistance by the examiner</i>			
	<i>5 = normal strength</i>			
<i>** Note: if total MRC score is &lt; 58, refer to muscle algorithm for patients management.</i>				
<i>Adapted from <a href="#">Kleyweg et al 1991</a>.</i>				

## **18 Appendix 6: Recommended pediatric dose of acetaminophen/paracetamol**

### **Usual Pediatric Dose for Fever**

#### **Infants and Children:**

IV: 2 to 12 years: 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours

Maximum single dose 15 mg/kg

Maximum total daily dose: 75 mg/kg/day not to exceed 3750 mg/day

Oral: 10 to 15 mg/kg/dose every 4 to 6 hours as needed; do not exceed 5 doses in 24 hours

Alternatively, the manufacturer lists the following recommended doses:

10.9 to 16.3 kg or 24 to 35 pounds: 2 to 3 years: 160 mg

16.4 to 21.7 kg or 36 to 47 pounds: 4 to 5 years: 240 mg

21.8 to 27.2 kg or 48 to 59 pounds: 6 to 8 years: 320 mg

27.3 to 32.6 kg or 60 to 71 pounds: 9 to 10 years: 400 mg

32.7 to 43.2 kg or 72 to 95 pounds: 11 years: 480 mg

The manufacturer recommends the use of weight to select the dose as the preferred method. If weight is not available, then age may be used.

Rectal: 10 to 20 mg/kg/dose every 4 to 6 hours as needed (Although the perioperative use of high dose rectal acetaminophen (e.g., 25 to 45 mg/kg/dose) has been investigated in several studies, its routine use remains controversial; optimal doses and dosing frequency to ensure efficacy and safety have not yet been established; further studies are needed).

#### **Children greater than or equal to 12 years:**

IV: Less than 50 kg: 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours

Maximum single dose: 750 mg/dose

Maximum total daily dose: 75 mg/kg/day (less than or equal to 3750 mg/day)

IV: Greater than or equal to 50 kg: 650 mg every 4 hours or 1000 mg every 6 hours

Maximum single dose: 1000 mg/dose

Maximum total daily dose: 4000 mg/day

Oral or Rectal: 325 to 650 mg every 4 to 6 hours or 1,000 mg 3 to 4 times daily

Maximum daily dose: 4000 mg/day

### **Usual Pediatric Dose for Pain**

#### **Infants and Children:**

IV: Less than 2 years: 7.5 to 15 mg/kg/dose every 6 hours

Maximum daily dose: 60 mg/kg/day

IV: 2 to 12 years: 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours

Maximum single dose 15 mg/kg

Maximum total daily dose: 75 mg/kg/day not to exceed 3750 mg/day

Oral: 10 to 15 mg/kg/dose every 4 to 6 hours as needed; do not exceed 5 doses in 24 hours

Alternatively, the manufacturer lists the following recommended doses:

10.9 to 16.3 kg or 24 to 35 pounds: 2 to 3 years: 160 mg

16.4 to 21.7 kg or 36 to 47 pounds: 4 to 5 years: 240 mg

21.8 to 27.2 kg or 48 to 59 pounds: 6 to 8 years: 320 mg

27.3 to 32.6 kg or 60 to 71 pounds: 9 to 10 years: 400 mg

32.7 to 43.2 kg or 72 to 95 pounds: 11 years: 480 mg

The manufacturer recommends the use of weight to select the dose as the preferred method. If weight is not available, then age may be used.

Rectal: 10 to 20 mg/kg/dose every 4 to 6 hours as needed (Although the perioperative use of high dose rectal acetaminophen (e.g., 25 to 45 mg/kg/dose) has been investigated in several studies, its routine use remains controversial; optimal doses and dosing frequency to ensure efficacy and safety have not yet been established; further studies are needed).

**Children greater than or equal to 12 years:**

IV: Less than 50 kg: 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours

Maximum single dose: 750 mg/dose

Maximum total daily dose: 75 mg/kg/day (less than or equal to 3750 mg/day)

IV: Greater than or equal to 50 kg: 650 mg every 4 hours or 1000 mg every 6 hours

Maximum single dose: 1000 mg/dose

Maximum total daily dose: 4000 mg/day

Oral or Rectal: 325 to 650 mg every 4 to 6 hours or 1,000 mg 3 to 4 times daily

Maximum daily dose: 4000 mg/day

(Accessed in Sep 2013:

<http://www.drugs.com/dosage/acetaminophen.html#ruMACzji6CtEOkhZ.99>)