



Clinical trial results:

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

Summary

EudraCT number	2012-004942-14
Trial protocol	GB GR BG
Global end of trial date	09 January 2019

Results information

Result version number	v2 (current)
This version publication date	21 September 2019
First version publication date	24 July 2019
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	CLDT600A2306
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02058108
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-000065-PIP01-07
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 January 2019
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	09 January 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective was 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.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 October 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 3
Country: Number of subjects enrolled	Greece: 1
Country: Number of subjects enrolled	Israel: 2
Country: Number of subjects enrolled	Korea, Republic of: 1
Country: Number of subjects enrolled	Romania: 18
Country: Number of subjects enrolled	Turkey: 17
Country: Number of subjects enrolled	Ukraine: 11
Worldwide total number of subjects	53
EEA total number of subjects	22

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23	0

months)	
Children (2-11 years)	29
Adolescents (12-17 years)	24
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted in 20 centers in 7 countries: Bulgaria (2), Greece (1), Israel (2), Republic of Korea (1), Romania (5), Turkey (4) and Ukraine (5 sites).

Pre-assignment

Screening details:

Patients were stratified by age group (2 to < 6 years, 6 to <12 years and 12 to <18 years) and HBV DNA level (low and high). At the baseline visit, eligible patients were randomized in a 24-week double blind period to telbivudine or placebo in a ratio 5:1. At Week 24 (visit 6), all patients were unblinded and HBV DNA level were assessed.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Telbivudine

Arm description:

Patients of any age and weight < 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 Patients < 12 years old and weight ≥ 30kg: telbivudine oral solution (20mg/mL), 600 mg/day corresponding to 30 mL p.o. once daily Patients ≥ 12 years old and weight ≥ 30kg: telbivudine film-coated tablet, 600 mg/day, corresponding to 1 tablet p.o. once daily

Arm type	Experimental
Investigational medicinal product name	Telbivudine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Patients of any age and weight < 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 Patients < 12 years old and weight ≥ 30kg: telbivudine oral solution (20mg/mL), 600 mg/day corresponding to 30 mL p.o. once daily

Investigational medicinal product name	Telbivudine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patients ≥ 12 years old and weight ≥ 30kg: telbivudine film-coated tablet, 600 mg/day, corresponding to 1 tablet p.o. once daily

Arm title	Placebo
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Arm description:

Patients of any age and weight < 30kg: placebo oral solution corresponding to weight (kg) x1mL, p.o. once daily Patients < 12 years old and weight ≥ 30kg: placebo oral solution corresponding to 30 mL p.o. once daily Patients ≥ 12 years old and weight ≥ 30kg: placebo tablet, corresponding to 1 tablet p.o. once daily. Placebo randomized patients were offered optional telbivudine administration at week 24.

Arm type	Placebo
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Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details:	
Placebo match to LDT600 600 mg film-coated tablets	
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use
Dosage and administration details:	
Placebo to match LDT600 20mg/mL oral solution	

Number of subjects in period 1	Telbivudine	Placebo
Started	43	10
Switched to Telbivudine after Week 24	0 ^[1]	5
Completed	2	0
Not completed	41	10
Consent withdrawn by subject	1	-
Abnormal Laboratory Values	-	1
Unsatisfactory therapeutic effect	37	4
Administrative problems	3	3
No longer requires study drug	-	1
Protocol deviation	-	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Placebo randomized patients were offered optional telbivudine administration at week 24. 5 Placebo randomized patients switched to Telbivudine after Week 24.

Baseline characteristics

Reporting groups

Reporting group title	Telvivudine
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Reporting group description:

Patients of any age and weight < 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 Patients < 12 years old and weight ≥ 30kg: telbivudine oral solution (20mg/mL), 600 mg/day corresponding to 30 mL p.o. once daily Patients ≥ 12 years old and weight ≥ 30kg: telbivudine film-coated tablet, 600 mg/day, corresponding to 1 tablet p.o. once daily

Reporting group title	Placebo
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Reporting group description:

Patients of any age and weight < 30kg: placebo oral solution corresponding to weight (kg) x1mL, p.o. once daily Patients < 12 years old and weight ≥ 30kg: placebo oral solution corresponding to 30 mL p.o. once daily Patients ≥ 12 years old and weight ≥ 30kg: placebo tablet, corresponding to 1 tablet p.o. once daily. Placebo randomized patients were offered optional telbivudine administration at week 24.

Reporting group values	Telvivudine	Placebo	Total
Number of subjects	43	10	53
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	23	6	29
Adolescents (12-17 years)	20	4	24
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous			
Units: Years			
arithmetic mean	10.2	9.1	
standard deviation	± 4.88	± 4.89	-
Sex: Female, Male			
Units: Subjects			
Female	14	4	18
Male	29	6	35
Race/Ethnicity, Customized			
Units: Subjects			
Caucasian	40	10	50
Black	1	0	1
Asian	2	0	2
Participants with alanine aminotransferase (ALT) - Multiples of upper limits of normal (ULN)			
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. Measurement at baseline.			
Units: Subjects			

< 1 × ULN	4	3	7
1 × - < 2 × ULN	22	4	26
2 × - < 5 × ULN	16	2	18
5 × or more ULN	1	1	2
Participants with aspartate aminotransferase (AST) - Multiples of upper limits of normal (ULN) Units: Subjects			
< 1 × ULN	26	5	31
1 × - < 2 × ULN	14	4	18
2 × - < 5 × ULN	2	0	2
5 × or more ULN	1	1	2
HBV DNA Units: log10 copies/mL arithmetic mean standard deviation	9.1 ± 1.14	8.2 ± 2.26	-

End points

End points reporting groups

Reporting group title	Telvivudine
Reporting group description: Patients of any age and weight < 30kg: telvivudine oral solution (20 mg/mL): 20 mg/kg up to 600 mg q.d corresponding to weight (kg) x1mL, p.o. once daily Patients < 12 years old and weight ≥ 30kg: telvivudine oral solution (20mg/mL), 600 mg/day corresponding to 30 mL p.o. once daily Patients ≥ 12 years old and weight ≥ 30kg: telvivudine film-coated tablet, 600 mg/day, corresponding to 1 tablet p.o. once daily	
Reporting group title	Placebo
Reporting group description: Patients of any age and weight < 30kg: placebo oral solution corresponding to weight (kg) x1mL, p.o. once daily Patients < 12 years old and weight ≥ 30kg: placebo oral solution corresponding to 30 mL p.o. once daily Patients ≥ 12 years old and weight ≥ 30kg: placebo tablet, corresponding to 1 tablet p.o. once daily. Placebo randomized patients were offered optional telvivudine administration at week 24.	

Primary: Number of patients achieving serum HBV DNA level of <300 copies/mL (51 IU/mL) at Week 24

End point title	Number of patients achieving serum HBV DNA level of <300 copies/mL (51 IU/mL) at Week 24
End point description: The primary objective of this study was to demonstrate the antiviral efficacy of telvivudine 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.	
End point type	Primary
End point timeframe: Week 24	

End point values	Telvivudine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	8		
Units: Participants				
number (not applicable)	5	1		

Statistical analyses

Statistical analysis title	Week 24 HBV DNA level of <300 copies/mL (51 IU/mL)
Statistical analysis description: HBV DNA level of <300 copies/mL (51 IU/mL) at Week 24	
Comparison groups	Telvivudine v Placebo

Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	
P-value	= 1
Method	Fisher exact
Parameter estimate	Mean difference (net)
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-37.03
upper limit	36.75

Secondary: Number of patients achieving HBV DNA< 300 copies/mL (51 IU/mL) at Week 52 and Week 104

End point title	Number of patients achieving HBV DNA< 300 copies/mL (51 IU/mL) at Week 52 and Week 104
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End point description:

The antiviral efficacy at Weeks 52 and 104 was to be evaluated by: a) the proportion of patients achieving HBV DNA <300 copies/mL (51 IU/mL) at Week 52 and Week 104; b) the proportion of patients achieving HBV DNA < Lower Limit of Quantification (LLOQ), <1000 copies/ml (or 200 IU/mL), <10,000 copies/ml (or 2 000 IU/mL) and ≥10,000 copies/mL (or 2 000 IU/mL) at Week 24, 52 and 104; c) the proportion of patients achieving Serum HBV DNA reduction from baseline; d) the time to achieve HBV DNA <300 copies/mL (51 IU/mL); e) the proportion of patients with Primary non-response. Due to early termination of the study and limited number of enrolled patients on track to complete 52 weeks of participation (8 patients overall), only descriptive analysis performed at Week 52 and Week 104.

End point type	Secondary
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End point timeframe:

Week 52, Week 104

End point values	Telbivudine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	3		
Units: Participants				
number (not applicable)				
Week 52	3	0		
Week 104	2	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients whose baseline ALTs were abnormal and subsequently normalized at Week 24, 52 and 104

End point title	Number of patients whose baseline ALTs were abnormal and
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subsequently normalized at Week 24, 52 and 104
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End point description:

The biochemical response at Weeks 24, 52 and 104 was to be evaluated by the proportion of patients whose baseline ALTs were abnormal (defined as ALT >1 x Upper Limit of Normal [ULN]) and subsequently normalized. Due to early termination of the study and limited number of enrolled patients on track to complete 52 weeks of participation (8 patients overall), only descriptive analysis performed at Week 52 and Week 104.

End point type

Secondary

End point timeframe:

Week 24, Week 52, Week 104

End point values	Telbivudine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	5		
Units: Participants				
number (not applicable)				
Week 24	12	0		
Week 52	1	1		
Week 104	2	0		

Statistical analyses**Statistical analysis title**

ALT levels at Week 24

Statistical analysis description:

ALT levels at Week 24

Comparison groups

Telbivudine v Placebo

Number of subjects included in analysis

42

Analysis specification

Pre-specified

Analysis type**P-value**

= 0.2984

Method

Fisher exact

Parameter estimate

Mean difference (net)

Point estimate

32.43

Confidence interval**level**

95 %

sides

2-sided

lower limit

-14.62

upper limit

74.6

Secondary: Number of patients with HBeAg loss, HBeAg seroconversion at Week 24, 52 and 104**End point title**

Number of patients with HBeAg loss, HBeAg seroconversion at Week 24, 52 and 104

End point description:

The serological response at Weeks 24, 52 and 104 was to be evaluated by: a) the proportion of HBeAg

positive patients at baseline who subsequently have HBeAg loss and HBeAg seroconversion (defined as loss of HBeAg with detectable HBeAb); b) the proportion of HBsAg positive patients at baseline who subsequently have HBsAg loss and HBsAg seroconversion (defined as loss of HBsAg with detectable HBsAb). Due to early termination of the study and limited number of enrolled patients on track to complete 52 weeks of participation (8 patients overall), only descriptive analysis performed at Week 52 and Week 104.

End point type	Secondary
End point timeframe:	
Week 24, Week 52, Week 104	

End point values	Telbivudine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	4		
Units: Participants				
number (not applicable)				
HBeAg loss at Week 24	1	0		
HBeAg seroconversion at Week 24	1	0		
HBeAg loss at Week 52	1	0		
HBeAg seroconversion at Week 52	1	0		
HBeAg loss at Week 104	1	0		
HBeAg seroconversion at Week 104	1	0		

Statistical analyses

Statistical analysis title	HBeAg loss at Week 24
Statistical analysis description:	
HBeAg loss at Week 24	
Comparison groups	Telbivudine v Placebo
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	
P-value	= 1
Method	Fisher exact
Parameter estimate	Mean difference (net)
Point estimate	2.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-53.7
upper limit	60.2

Statistical analysis title	HBeAg seroconversion at Week 24
Statistical analysis description:	
HBeAg seroconversion at Week 24	
Comparison groups	Telbivudine v Placebo

Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	
P-value	= 1
Method	Fisher exact
Parameter estimate	Mean difference (net)
Point estimate	2.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-53.7
upper limit	60.2

Secondary: Number of patients with HBsAg loss, HBsAg seroconversion at Week 24, 52 and 104

End point title	Number of patients with HBsAg loss, HBsAg seroconversion at Week 24, 52 and 104
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End point description:

The serological response at Weeks 24, 52 and 104 was to be evaluated by: a) the proportion of HBeAg positive patients at baseline who subsequently have HBeAg loss and HBeAg seroconversion (defined as loss of HBeAg with detectable HBeAb); b) the proportion of HBsAg positive patients at baseline who subsequently have HBsAg loss and HBsAg seroconversion (defined as loss of HBsAg with detectable HBsAb). Due to early termination of the study and limited number of enrolled patients on track to complete 52 weeks of participation (8 patients overall), only descriptive analysis performed at Week 52 and Week 104.

End point type	Secondary
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End point timeframe:

Week 24, Week 52, Week 104

End point values	Telbivudine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	7		
Units: Participants				
number (not applicable)				
HBsAg loss at Week 24	1	0		
HBsAg seroconversion at Week 24	0	0		
HBsAg loss at Week 52	0	0		
HBsAg seroconversion at Week 52	0	0		
HBsAg loss at Week 104	0	0		
HBsAg seroconversion at Week 104	0	0		

Statistical analyses

Statistical analysis title	HBsAg loss at Week 24
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Statistical analysis description:

HBsAg loss at Week 24

Comparison groups	Telbivudine v Placebo
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	
P-value	= 1
Method	Fisher exact
Parameter estimate	Mean difference (net)
Point estimate	2.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-37.54
upper limit	42.17

Secondary: Number of patients achieving a composite endpoints (HBV DNA < 300 copies/mL (51 IU/mL), ALT normalization and HBeAg seroconversion) at Week 52 and 104

End point title	Number of patients achieving a composite endpoints (HBV DNA < 300 copies/mL (51 IU/mL), ALT normalization and HBeAg seroconversion) at Week 52 and 104
End point description:	The proportion of patients achieving composite endpoints at Week 52 and 104 was to be evaluated by the proportion of patients achieving: a) HBV DNA <300 copies/mL (51 IU/mL); b) ALT normalization and HBeAg seroconversion for HBeAg positive patients only; c) HBV DNA <300 copies/mL (51 IU/mL) and ALT normalization for HBeAg negative patients. Due to early termination of the study and limited number of enrolled patients on track to complete 52 weeks of participation (8 patients overall), only descriptive analysis performed at Week 52 and Week 104.
End point type	Secondary
End point timeframe:	
Week 52, Week 104	

End point values	Telbivudine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	3		
Units: Participants				
number (not applicable)				
Week 52	1	0		
Week 104	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients achieving cumulative rate of virological breakthrough (VB) at Week 52 and 104

End point title	Number of patients achieving cumulative rate of virological
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End point description:

The assessment of virological breakthrough (VB) was to be evaluated by: a) the cumulative rate of patients with confirmed VB at Week 52 and Week 104; b) the time to VB. Due to early termination of the study and limited number of enrolled patients on track to complete 52 weeks of participation (8 patients overall), only descriptive analysis performed at Week 52 and Week 104.

End point type

Secondary

End point timeframe:

Week 52, Week 104

End point values	Telbivudine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	8		
Units: Participants				
number (not applicable)				
Week 52	1	0		
Week 104	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with treatment emergent genotypic resistance associated with VB, or in patients with HBV DNA $\geq$ 300 copies/mL (51 IU/mL) at Week 24 and discontinued from the study

End point title

Number of Participants with treatment emergent genotypic resistance associated with VB, or in patients with HBV DNA $\geq$ 300 copies/mL (51 IU/mL) at Week 24 and discontinued from the study

End point description:

Assessment of the presence of treatment emergent genotypic resistance (confirmed by genotypic sequencing) 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)

End point type

Secondary

End point timeframe:

Week 24

End point values	Telbivudine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	8		
Units: Participants				
number (not applicable)				
Cumulative virological breakthrough	0	0		
Cumulative treatment emergent genotypic resistance	1	0		

Statistical analyses

Statistical analysis title	Treatment emergent genotypic resistance at Week 24
Statistical analysis description: Treatment emergent genotypic resistance at Week 24	
Comparison groups	Telbivudine v Placebo
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	
P-value	= 1
Method	Fisher exact
Parameter estimate	Mean difference (net)
Point estimate	2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-37.05
upper limit	41.83

Secondary: Number of Participants with On-Treatments Adverse Events, Serious Adverse Events, and Death

End point title	Number of Participants with On-Treatments Adverse Events, Serious Adverse Events, and Death
End point description: Evaluation of the safety and tolerability of Telbivudine 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. Only descriptive analysis performed.	
End point type	Secondary
End point timeframe: From first dose of study treatment to 30 days after last dose of study treatment, up to 112 weeks	

End point values	Telbivudine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	10		
Units: Participants				
number (not applicable)				
On-treatment Adverse Event (AEs)	20	4		
On-treatment Serious Adverse Event (SAEs)	0	0		

On-treatment Deaths	0	0		
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Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events and serious adverse events were collected for the maximum actual duration of treatment exposure and follow up for a participant per the protocol for approximately 112 weeks.

Adverse event reporting additional description:

AEs occurring in patients in the Initial Placebo group were assigned to either Placebo or Telbivudine (LdT) treatment based on their onset date:

- Placebo: AEs with onset before the first date of LdT treatment after switching+patients who did not switch to LdT
- LdT: AEs with onset date on or after the first date of LdT treatment after switching

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Initial Ldt
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Reporting group description:

Initial Ldt

Reporting group title	On Placebo
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Reporting group description:

On Placebo

Reporting group title	On Ldt
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Reporting group description:

On Ldt

Reporting group title	All Ldt
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Reporting group description:

All Ldt

Serious adverse events	Initial Ldt	On Placebo	On Ldt
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 43 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	All Ldt		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 48 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Initial Ldt	On Placebo	On Ldt
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 43 (46.51%)	4 / 10 (40.00%)	1 / 5 (20.00%)
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	2 / 43 (4.65%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Surgical and medical procedures			
Antibiotic prophylaxis			
subjects affected / exposed	0 / 43 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 43 (2.33%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	6 / 43 (13.95%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	7	1	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 43 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Conjunctival hyperaemia			
subjects affected / exposed	1 / 43 (2.33%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 43 (2.33%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Abdominal pain upper			
subjects affected / exposed	5 / 43 (11.63%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	6	0	0
Diarrhoea			

subjects affected / exposed occurrences (all)	2 / 43 (4.65%) 2	0 / 10 (0.00%) 0	0 / 5 (0.00%) 0
Nausea subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0	1 / 10 (10.00%) 1	0 / 5 (0.00%) 0
Vomiting subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1	0 / 10 (0.00%) 0	0 / 5 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1	0 / 10 (0.00%) 0	0 / 5 (0.00%) 0
Epistaxis subjects affected / exposed occurrences (all)	2 / 43 (4.65%) 2	0 / 10 (0.00%) 0	0 / 5 (0.00%) 0
Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1	0 / 10 (0.00%) 0	0 / 5 (0.00%) 0
Infections and infestations Exanthema subitum subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1	0 / 10 (0.00%) 0	0 / 5 (0.00%) 0
Gastroenteritis subjects affected / exposed occurrences (all)	2 / 43 (4.65%) 2	0 / 10 (0.00%) 0	0 / 5 (0.00%) 0
Laryngitis subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1	0 / 10 (0.00%) 0	0 / 5 (0.00%) 0
Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0	0 / 10 (0.00%) 0	1 / 5 (20.00%) 1
Otitis media subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1	0 / 10 (0.00%) 0	0 / 5 (0.00%) 0
Pharyngitis			

subjects affected / exposed	1 / 43 (2.33%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Tonsillitis			
subjects affected / exposed	1 / 43 (2.33%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 43 (2.33%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Varicella			
subjects affected / exposed	1 / 43 (2.33%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Viral infection			
subjects affected / exposed	1 / 43 (2.33%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Viral upper respiratory tract infection			
subjects affected / exposed	3 / 43 (6.98%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	3	0	0

Non-serious adverse events	All Ldt		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 48 (43.75%)		
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	2 / 48 (4.17%)		
occurrences (all)	2		
Surgical and medical procedures			
Antibiotic prophylaxis			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	6 / 48 (12.50%)		
occurrences (all)	7		
Ear and labyrinth disorders			

Ear pain subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0		
Eye disorders Conjunctival hyperaemia subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1 5 / 48 (10.42%) 6 2 / 48 (4.17%) 2 0 / 48 (0.00%) 0 1 / 48 (2.08%) 1		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1 2 / 48 (4.17%) 2		
Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1		
Infections and infestations			

Exanthema subitum			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	2 / 48 (4.17%)		
occurrences (all)	2		
Laryngitis			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Otitis media			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Pharyngitis			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Tonsillitis			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Varicella			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Viral infection			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Viral upper respiratory tract infection			
subjects affected / exposed	3 / 48 (6.25%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 March 2015	Amendment 1 was issued after the inclusion of 35.3% of patients and introduced the following changes: • 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 CHB infection for the specified age groups (which eliminated children 12 years of age or older from study participation in South Korea). • Clarify serum ALT criteria for study inclusion. Eliminate the inclusion criterion for patients with normal ALT levels to substantiate moderate to severe hepatic inflammation by histology report or FibroScan. • Eliminate acute infection with herpes simplex virus (HSV) as exclusion criteria. • Eliminate duplication of list of viral causes of infectious hepatitis (Exclusion Criteria 7 and 12). • Clarify the management of patient discontinuation and premature patient withdrawal. • Remove the Serum ALT requirements for eligibility criteria for placebo treated patients to start telbivudine treatment at Week 28. • 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. • Extend screening period up to 10 weeks in cases of operational or administrative issues.
22 November 2016	Amendment 2 was issued at that time enrolment was already placed on temporary halt. It added clarifications on the role of Data Monitoring Committee (DMC) and add clarifying wording for the timing of interim analyses. Amendment stated while planned DMC convened regularly to review safety analyses, committee could also request and review additional safety and /or efficacy analyses where appropriate.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to early termination of the study and limited number of enrolled patients on track to complete 52 weeks of participation (8 patients overall), no formal analysis of Weeks 52 and 104 long-term efficacy endpoints (only descriptive analysis).

Notes: