Clinical trial results:
A Phase I, Open-Label, Single-Dose Study to Evaluate the Pharmacokinetics and Safety of Telbivudine (LdT) in Children and Adolescents with Chronic Hepatitis B Virus Infection

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.novfor complete trial results.

Summary

EudraCT number	2007-006218-40
Trial protocol	BE DE GB BG Outside EU/EEA
Global end of trial date	27 November 2011

Results information

Result version number	v1 (current)
This version publication date	06 July 2018
First version publication date	06 July 2018

Trial information

Trial identification

Sponsor protocol code	CLDT600A2104

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00907894
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 ,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, +41 613241111 ,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-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	27 November 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 November 2011
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to evaluate the single-dose pharmacokinetics, safety and tolerability of Telbivudine (15mg/kg, 25mg/kg and 600mg) oral solution in pediatric and adolescent subjects (aged 2 to 18 years) infected with chronic hepatitis B (CHB) virus infection.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 February 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Bulgaria: 4
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Egypt: 2
Country: Number of subjects enrolled	Philippines: 7
Worldwide total number of subjects	23
EEA total number of subjects	14

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 months)	0
Children (2-11 years)	15
Adolescents (12-17 years)	8
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 6 centres in 6 countries.

Pre-assignment

Screening details:

A total of 23 subjects infected with Hepatitis B Virus (HBV) were enrolled in the study. Based on their age, the subjects were stratified to 3 stratums. i.e Stratum 1: 2 to less than 6 years old, Stratum 2: 6 to less than 12 years old and Stratum 3: 13 to 18 years old subjects.

Period 1

Period 1 title	Overall Period (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This was an open-label study, hence no blinding was implemented.

Arms

Are arms mutually exclusive?	Yes
Arm title	Telbivudine 15 mg/kg

Arm description:

Single dose of telbivudine 15 mg/kg oral solution was administered once daily to subjects stratified by age (2-<6 years and 6-<12 years).

Arm type	Experimental
Investigational medicinal product name	Telbivudine 15 mg/kg
Investigational medicinal product code	LDT600
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Single dose of telbivudine 15 mg/kg oral solution was administered once daily.

Arm title	Telbivudine 25 mg/kg

Arm description:

Single dose of telbivudine 25 mg/kg oral solution was administered once daily to subjects stratified by age (2-<6 years and 6-<12 years).

Arm type	Experimental
Investigational medicinal product name	Telbivudine 25 mg/kg
Investigational medicinal product code	LDT600
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Single dose of telbivudine 25 mg/kg oral solution was administered once daily.

Arm title	Telbivudine 600 mg

Arm description:

Single dose of telbivudine 600 mg oral solution was administered once daily to subjects stratified by age (13 to 18 years).

Arm type	Experimental

Investigational medicinal product name	Telbivudine 600 mg
Investigational medicinal product code	LDT600
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Single dose of telbivudine 600 mg oral solution was administered once daily.

Number of subjects in period 1	Telbivudine 15 mg/kg	Telbivudine 25 mg/kg	Telbivudine 600 mg
Started	10	5	8
Completed	10	5	8

Baseline characteristics

Reporting groups	
Reporting group title	Overall Period

Reporting group description: -

Reporting group values	Overall Period	Total	
Number of subjects	23	23	
Age categorical Units: Subjects			
Children (2-<6 years)	7	7	
Children (6-12 years)	8	8	
Adolescents (13-18 years)	8	8	
Age continuous Units: years			
arithmetic mean	9.4		
standard deviation	± 4.99	-	
Gender categorical Units: Subjects			
Female	11	11	
Male	12	12	

End points

End points reporting groups

Reporting group title	Telbivudine 15 mg/kg
Reporting group description:	
Single dose of telbivudine 15 mg/kg oral solution was administered once daily to subjects stratified by age (2-<6 years and 6-<12 years).	
Reporting group title	Telbivudine 25 mg/kg
Reporting group description:	
Single dose of telbivudine 25 mg/kg oral solution was administered once daily to subjects stratified by age (2-<6 years and 6-<12 years).	
Reporting group title	Telbivudine 600 mg
Reporting group description:	
Single dose of telbivudine 600 mg oral solution was administered once daily to subjects stratified by age (13 to 18 years).	

Primary: Maximum Observed Plasma Concentration (Cmax)

End point title	Maximum Observed Plasma Concentration (Cmax)[1]
End point description:	
Maximum observed plasma concentration following drug administration from the raw plasma concentration-time data. Analysis was performed in pharmacokinetic (PK) set population which included the subjects with evaluable PK data and no major protocol deviations with impact on PK data. The 'n' signifies those subjects evaluable for this measure for each strata based on age stratification by reporting group, respectively. For n=0, data "0.0" is reported because , EudraCT system is not allowing to report "NA" for not applicable/not available data.	
End point type	Primary
End point timeframe:	
Pre-dose (0), 1, 2, 3, 4, 8, 12, 24, 32, 48, 72 and 120 hours post-dose	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics only

End point values	Telbivudine 15 mg/kg	Telbivudine 25 mg/kg	Telbivudine 600 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10[2]	5[3]	8[4]	
Units: nanogram/millilitre(ng/mL)				
arithmetic mean (standard deviation)				
Stratum 1: 2-<6 years old (n=6,1,0)	2910 (± 453)	2440 (± 0)	0 (± 0)	
Stratum 2: 6-<12 years old (n =4,4,0)	3290 (± 748)	5430 (± 1530)	0 (± 0)	
Stratum 3:13-18 years old (n =0,0,8)	0 (± 0)	0 (± 0)	3510 (± 1190)	

Notes:

[2] - Data should be "NA" for Stratum 3 as n=0, reported '0' to avoid invalid system error

[3] - Data should be "NA" for Stratum 3 as n=0, reported '0' to avoid invalid system error

[4] - Data should be "NA" for Stratum 1 and 2 as n=0, reported '0' to avoid invalid system error

Statistical analyses

No statistical analyses for this end point

Primary: Area under the drug concentration-time curve from time zero to 24 hours after dosing(AUC0-24h)

End point title	Area under the drug concentration-time curve from time zero to 24 hours after dosing(AUC0-24h)[5]

End point description:

AUC(0-24h) was defined as the area under the drug concentration-time curve calculated using linear trapezoidal summation from time zero to 24 hours after dosing. Analysis was performed in PK set population. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively. For n=0, data "0" is reported because , EudraCT system is not allowing to report "NA" for not applicable/not available data.

End point type	Primary

End point timeframe:

Pre-dose (0), 1, 2, 3, 4, 8, 12 and 24 hours post-dose

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics only

End point values	Telbivudine 15 mg/kg	Telbivudine 25 mg/kg	Telbivudine 600 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10[6]	5[7]	8[8]	
Units: nanogram.hour/milliLitre(ng.hr/mL)				
arithmetic mean (standard deviation)				
Stratum 1: 2-<6 years old (n=6,1,0)	17900 (± 3550)	15300 (± 0)	0 (± 0)	
Stratum 2: 6-<12 years old (n =4,4,0)	17600 (± 3400)	33100 (± 9530)	0 (± 0)	
Stratum 3:13-18 years old (n =0,0,8)	0 (± 0)	0 (± 0)	22300 (± 5720)	

Notes:

[6] - The data was not applicable for Stratum 3 and denoted as 0.

[7] - The data was not applicable for Stratum 3 and denoted as 0.

[8] - The data was not applicable for Stratum 1 and Stratum 2 and denoted as 0.

Statistical analyses

No statistical analyses for this end point

Primary: AUC From Time Zero to Last Measurable Concentration [AUC (0-t)]

End point title	AUC From Time Zero to Last Measurable Concentration [AUC (0-t)][9]

End point description:

Area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration. It was calculated as the sum of linear trapezoids using non-compartmental analysis. Analysis was performed in PK set population. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively. For n=0, data "0" is reported because , EudraCT system is not allowing to report "NA" for not applicable/not available data.

End point type	Primary

End point timeframe:

Pre-dose (0), 1, 2, 3, 4, 8, 12, 24, 32, 48, 72 and 120 hours post-dose

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics only

End point values	Telbivudine 15 mg/kg	Telbivudine 25 mg/kg	Telbivudine 600 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10[10]	5[11]	8[12]	
Units: hr.ng/mL				
arithmetic mean (standard deviation)				
Stratum 1: 2-<6 years old (n=6,1,0)	21200 (± 4520)	19900 (± 0)	0 (± 0)	
Stratum 2: 6-<12 years old (n =4,4,0)	20700 (± 4550)	39700 (± 9760)	0 (± 0)	
Stratum 3:13-18 years old (n =0,0,8)	0 (± 0)	0 (± 0)	26800 (± 6590)	

Notes:

[10] - The data was not applicable for Stratum 3 and denoted as 0.

[11] - The data was not applicable for Stratum 3 and denoted as 0.

[12] - The data was not applicable for Stratum 1 and Stratum 2 and denoted as 0.

Statistical analyses

No statistical analyses for this end point

Primary: AUC From Time Zero to Extrapolated Infinite Time [AUC (0 - ∞)]

End point title	AUC From Time Zero to Extrapolated Infinite Time [AUC (0 - ∞)][13]

End point description:

AUC (0 - ∞)= Area under the plasma concentration versus time curve (AUC) from time zero (pre-dose) to extrapolated infinite time (0 - ∞). AUC(0-infinity) was estimated as AUC 0-t + C t /λ z, where λ z was the terminal elimination rate constant. Analysis was performed in PK set population. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively. For n=0, data "0" is reported because , EudraCT system is not allowing to report "NA" for not applicable/not available data.

End point type	Primary

End point timeframe:

Pre-dose (0), 1, 2, 3, 4, 8, 12, 24, 32, 48, 72 and 120 hours post-dose

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics only

End point values	Telbivudine 15 mg/kg	Telbivudine 25 mg/kg	Telbivudine 600 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10[14]	5[15]	8[16]	
Units: hr.ng/mL				
arithmetic mean (standard deviation)				
Stratum 1: 2-<6 years old (n=6,1,0)	22100 (± 4760)	20400 (± 0)	0 (± 0)	
Stratum 2: 6-<12 years old (n =4,4,0)	21500 (± 4610)	40500 (± 9680)	0 (± 0)	
Stratum 3:13-18 years old (n =0,0,8)	0 (± 0)	0 (± 0)	27700 (± 6830)	

Notes:

[14] - The data was not applicable for Stratum 3 and denoted as 0.

[15] - The data was not applicable for Stratum 3 and denoted as 0.

[16] - The data was not applicable for Stratum 1 and Stratum 2 and denoted as 0.

Statistical analyses

No statistical analyses for this end point

Primary: Oral Total Plasma Clearance (CL/F)

End point title	Oral Total Plasma Clearance (CL/F)[17]

End point description:

Oral total plasma clearance (CL/F) was calculated as Dose/AUC0-∞, where CL was the clearance of the drug and F was the absolute oral bioavailability. Analysis was performed in PK set population. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively. For n=0, data "0" is reported because , EudraCT system is not allowing to report "NA" for not applicable/not available data.

End point type	Primary

End point timeframe:

Pre-dose(0), 1, 2, 3, 4, 8, 12, 24, 32, 48, 72 and 120 hours post-dose

Notes:

[17] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics only

End point values	Telbivudine 15 mg/kg	Telbivudine 25 mg/kg	Telbivudine 600 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10[18]	5[19]	8[20]	
Units: milliletre (mL)/hour(hr)				
arithmetic mean (standard deviation)				
Stratum 1: 2-<6 years old (n=6,1,0)	15200 (± 5920)	17100 (± 0)	0 (± 0)	
Stratum 2: 6-<12 years old (n =4,4,0)	19200 (± 2060)	15000 (± 3820)	0 (± 0)	
Stratum 3:13-18 years old (n =0,0,8)	0 (± 0)	0 (± 0)	23200 (± 7660)	

Notes:

[18] - The data was not applicable for Stratum 3 and denoted as 0.

[19] - The data was not applicable for Stratum 3 and denoted as 0.

[20] - The data was not applicable for Stratum 1 and Stratum 2 and denoted as 0.

Statistical analyses

No statistical analyses for this end point

Primary: Terminal Half-Life

End point title	Terminal Half-Life[21]

End point description:

Terminal half-life was the time required for one half of the total amount of administered drug eliminated from the body. Analysis was performed in PK set population. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively. For n=0, data "0" is reported because , EudraCT system is not allowing to report "NA" for not applicable/not available data.

End point type	Primary

End point timeframe:

Pre-dose(0), 1, 2, 3, 4, 8, 12, 24, 32, 48, 72 and 120 hours post-dose

Notes:

[21] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics only

End point values	Telbivudine 15 mg/kg	Telbivudine 25 mg/kg	Telbivudine 600 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10[22]	5[23]	8[24]	
Units: hr				
arithmetic mean (standard deviation)				
Stratum 1: 2-<6 years old (n=6,1,0)	29.9 (± 10.5)	28.3 (± 0)	0 (± 0)	
Stratum 2: 6-<12 years old (n =4,4,0)	36.3 (± 6.81)	28 (± 7.03)	0 (± 0)	
Stratum 3:13-18 years old (n =0,0,8)	0 (± 0)	0 (± 0)	38.7 (± 7.42)	

Notes:

[22] - The data was not applicable for Stratum 3 and denoted as 0

[23] - The data was not applicable for Stratum 3 and denoted as 0

[24] - The data was not applicable for Stratum 1 and Stratum 2 and denoted as 0.

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with adverse events (AEs) and serious adverse events (SAEs)

End point title	Number of subjects with adverse events (AEs) and serious adverse events (SAEs)[25]

End point description:

An AE was defined as any unfavorable and unintended sign, symptom, or disease temporally associated with the use of study drug, whether or not related to study drug. A SAE was defined as an event which was fatal or life threatening, required or prolonged hospitalization, was significantly or permanently disabling or incapacitating, constituted a congenital anomaly or a birth defect, or encompassed any other clinically significant event that could jeopardize the subject or require medical or surgical intervention to prevent one of the aforementioned outcomes. All the subjects received study drug were included in the safety analysis set.

End point type	Primary

End point timeframe:

From first patient first treatment up to 30 days following the end of study

Notes:

[25] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive only

End point values	Telbivudine 15 mg/kg	Telbivudine 25 mg/kg	Telbivudine 600 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	5	8	
Units: Number				
AEs	1	0	3	
SAEs	0	0	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	LDT600 15 mg/kg solution

Reporting group description:

Single dose of telbivudine 15mg/kg oral solution was administered once daily to subjects stratified by age (2-<6 years and 6-<12 years).

Reporting group title	LDT600 600 mg solution

Reporting group description:

Single dose of telbivudine 600 mg oral solution was administered once daily to subjects stratified by age (13 to 18 years).

Reporting group title	Telbivudine 25 mg/kg

Reporting group description:

Single dose of telbivudine 25 mg/kg oral solution was administered once daily to subjects stratified by age (2-<6 years and 6-<12 years).

Serious adverse events	LDT600 15 mg/kg solution	LDT600 600 mg solution	Telbivudine 25 mg/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	0 / 5 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	LDT600 15 mg/kg solution	LDT600 600 mg solution	Telbivudine 25 mg/kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 10 (10.00%)	3 / 8 (37.50%)	0 / 5 (0.00%)
Investigations			
PROTEIN URINE PRESENT			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0

Injury, poisoning and procedural complications			
POST PROCEDURAL DISCOMFORT			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
CHILLS			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
MALAISE			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
DIARRHOEA			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
PRURITUS			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
SKIN LESION			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Infections and infestations			
NASOPHARYNGITIS			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	0 / 5 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 September 2007	1) Day 2 clinical laboratory assessments and 32 hour post dose sampling were removed 2) The methods for subject stratification were changed to include substrata 3) Elements of inclusion and exclusion criteria were revised 4) Subjects vomiting within the first 3 hours after dosing were to be withdrawn and replaced. 5)The time period for adverse event follow up was modified
16 January 2008	1) Change of serious adverse event and adverse event reporting process 2) Clarification of strata dosing sequence 3) Additional information provided in dose selection section 4) Removal of the drug preparation procedure from the protocol 5) Addition of pregnancy reporting process 6) Addition of pharmacokinetic sample numbers.
30 May 2008	1) Change of serious adverse event reporting 2) Additional instruction for use of study drug

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.

Study was terminated after enrollment of 23 of the planned 28 patients as it had met its primary objective, enrollment was slower than anticipated, and health authorities agreed with the sponsor’s dosing proposal from the study data.

Notes: