Sponsor

Novartis

Generic Drug Name

Telbivudine

Therapeutic Area of Trial

Chronic Hepatitis B

Approved Indication

Chronic Hepatitis B

Protocol Number

CLDT600A2104

Title

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

Phase of Development

1

Study Start/End Dates

05-Feb-2009/08-Mar-2012

Early termination date: 08-Mar-2012

The Study was closed early after consultation with Health Authorities that sufficient data to support a dosing recommendation had been collected and challenge of recruiting pediatric patients.

Study Design/Methodology

Multi-center, open label, non-randomized, stratified study design. Patients were enrolled by stratum as follows

- Stratum 3: 13-18 years old.
- Stratum 2: 6-12 years old
  Substrata 6- <9 year and 9-12 year;
- Stratum 1: 2- <6 years old
  Substrata 2- <4 year and 4- <6 year;

Eligible patients received a single dose of study medication followed by blood collections for safety and pharmacokinetic determinations. Patients were confined from either Day -1 or Day 1 dosing through the 24-hour plasma pharmacokinetic (PK) sample drawn on Day 2. After

discharge from the inpatient stay, plasma blood samples were obtained on an outpatient basis on Days 3, 4 and 6.

Adolescent subjects in Stratum 3 received a single dose of 600 mg LDT600 as an oral solution. The first half (n=4) of Stratum 2 received a single 15 mg/kg dose of LDT600 as an oral solution following review of Stratum 3 safety and pharmacokinetic parameters. The second half (n=4) of Stratum 2 and the first half of Stratum 1 (n=6) will received a single 25mg/kg and 15 mg/kg dose of LDT600, respectively, as an oral solution following review of Stratum 2 (n=4) safety and pharmacokinetic parameters. The remaining patients in Stratum 1 (n=6) will received a 25 mg/kg dose of LDT600 as an oral solution following review of Stratum 1 safety and pharmacokinetic parameters.

Centres

Belgium (1), Philippines (2), Germany (3), UK (2), Egypt (1), Bulgaria (2)

Publication

None

Outcome measures

Primary outcome measures(s)

- To evaluate the single-dose pharmacokinetics of LDT600 in pediatric and adolescent patients with chronic HBV (CHB) infection
- To evaluate the safety and tolerability of LDT600 in pediatric and adolescent patients with CHB infection.

Test Product (s), Dose(s), and Mode(s) of Administration

LDT600 administered orally.
Doses were 600 mg, 25 mg/kg or 15 mg/kg

Statistical Methods

PK parameters are summarized using descriptive statistics (arithmetic mean, median, SD, SEM, CV%, sample size, minimum, and maximum, where applicable). Summaries will be presented by age Stratum.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria:

1. Patients or legal guardian must have read and signed the written informed consent form (ICF) after the nature of the study has been fully explained and all questions answered.
2. Patients must be between the ages of 2 to 18 years with body weight within 15th to 85th percentile of normal relative to age, based on either the Centers for Disease Control and Prevention (CDC) growth chart or national health service norms.
3. The patient must have documented chronic HBV (CHB) infection with positive HbsAg assay at Screening.
4. Patients must have a screening creatinine clearance (CLcr) ⩾ 80 mL/min/1.73 m2 as estimated by the Schwartz formula (See Section 9.7.6.6).

Exclusion Criteria:

1. Decompensated liver disease (Child-Turcotte-Pugh (CTP) Score≥7, Class B and C)
2. Other clinically significant disease, condition or abnormality, unrelated to their HBV infection, as assessed by the Investigator, based on medical history, physical examination, 12-lead electrocardiogram (ECG), or clinical laboratory testing, including:
   - Hemoglobin value <110 g/L (11.0 g/dL) for males and <100 g/L (10.0 g/dL) for females
   - Absolute neutrophil count (ANC) (<1,500/ x $10E^3$) (<1.5x$10E^9$)
   - Platelet count (< 120,000/ x$10E^3$) (<120 x$10E^9$)
   - White blood cell count (WBC) (<3,000/ x$10E^3$) (3.0 x$10E^9$)
   - Prothrombin time/INR prolonged by more than 3 seconds, (based on the Upper Limit Normal [ULN]; of the reference value)
   - Serum amylase or lipase ⩾1.5 x ULN;
   - Serum albumin (<3.5 g/dL); (<35 g/L)
   - Total bilirubin (⩾2.0 mg/dL or ⩾34.2 µmol/L);
   - Serum ALT level >10 x ULN.
   - Blood urea nitrogen (BUN) greater than the upper limit of normal.
3. Treatment with interferon within six months of Screening.
4. Treatment with nucleoside/nucleotide reverse transcriptase inhibitors within three months of Screening.
5. Treatment with any other anti-HBV drugs or other antiviral therapy (e.g., acyclovir ganciclovir) within 30 days of study drug dosing.

Participant Flow

	LDT600 15mg/kg N=10	LDT600 25mg/kg N=5	LDT600 600mg N=8	All Treatments N=23
Patients				
Completed	10 (100.0)	5 (100.0)	8 (100.0)	23 (100.0)

Baseline Characteristics

Demographic Variable	2-<6 years old N=7	6-12 years old N=8	13-18 years old N=8
Age (years)			
Mean (SD)	3.9 (1.46)	8.5 (2.07)	15.3 (1.16)
Median	5.0	8.5	15.5
Range	2-5	6-11	14-17
Height (cm)			
Mean (SD)	107.1 (18.21)	132.3 (13.45)	162.4 (9.07)
Median	114.0	129.5	165.0
Range	82-128	115-156	149-173
Weight (kg)			
Mean (SD)	20.13 (6.879)	30.44 (7.983)	57.10 (10.364)
Median	20.00	29.50	60.40
Range	13.0-32.0	21.0-45.2	40.0-67.0
BMI (kg/m^2)			
Mean (SD)	17.260 (2.0928)	17.083 (1.4948)	21.653 (3.8539)
Median	17.654	16.729	20.628
Range	14.78-19.53	14.83-19.19	17.78-29.59
Gender – n(%)			
Male	2 (28.6 %)	4 (50.0 %)	6 (75.0 %)
Female	5 (71.4 %)	4 (50.0 %)	2 (25.0 %)
Race – n(%)			
Caucasian	6 (85.7 %)	3 (37.5 %)	2 (25.0 %)
Asian	1 (14.3 %)	4 (50.0 %)	6 (75.0 %)
Other		1 (12.5 %)	

Outcome measures

Primary Outcome Result

pharmacokinetics of LDT600

PK parameter	T_{max} (h)	C_{max} (ng/mL)	AUC_{0-24h} (ng.h/mL)	AUC_{0-t} (ng.h/mL)	AUC_{inf} (ng.h/mL)	$T_{1/2}$ (h)	CL/F (mL/hr)

13-18 years 600 mg; n=8							
Mean	-	3510	22300	26800	27700	38.7	23200
SD	-	1190	5720	6590.	6830	7.42	7660
6-12 years 15 mg/kg; n=4							
Mean	-	3290	17600	20700	21500	36.3	19200
SD	-	748	3400	4550	4610	6.81	2060
6-12 years 25 mg/kg; n=4							
Mean	-	5430	33100	39700	40500	28.0	15000
SD	-	1530	9530	9760	9680	7.03	3820
2-<6 years 15 mg/kg; n=6							
Mean	-	2910	17900	21200	22100	29.9	15200
SD	-	453	3550	4520	4760	10.5	5920
2-<6 years 25 mg/kg; n=1							
Mean	4.00	2440	15300	19900	20400	28.3	17100

Safety Results

	LDT600 15mg/kg N=10 n (%)	**LDT600 25mg/kg N=5 n (%)**	**LDT600 600mg N=8 n (%)**
Patients with AE(s)	1 (10.0)	0 (0.0)	3 (37.5)
System organ class			
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0 (0.0)	0 (0.0)	2 (25.0)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (10.0)	0 (0.0)	1 (12.5)
GASTROINTESTINAL DISORDERS	0 (0.0)	0 (0.0)	1 (12.5)
INFECTIONS AND INFESTATIONS	0 (0.0)	0 (0.0)	1 (12.5)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0 (0.0)	0 (0.0)	1 (12.5)
INVESTIGATIONS	1 (10.0)	0 (0.0)	0 (0.0)

Most Frequently Reported AEs Overall by Preferred Term n (%)

	LDT600 15mg/kg N=10 n (%)	LDT600 25mg/kg N=5 n (%)	LDT600 600mg N=8 n (%)
Patients with AE(s)	1 (10.0)	0 (0.0)	3 (37.5)
Preferred term			
CHILLS	0 (0.0)	0 (0.0)	1 (12.5)
DIARRHOEA	0 (0.0)	0 (0.0)	1 (12.5)
MALAISE	0 (0.0)	0 (0.0)	1 (12.5)
NASOPHARYNGITIS	0 (0.0)	0 (0.0)	1 (12.5)
POST PROCEDURAL DISCOMFORT	0 (0.0)	0 (0.0)	1 (12.5)
PROTEIN URINE PRESENT	1 (10.0)	0 (0.0)	0 (0.0)
PRURITUS	0 (0.0)	0 (0.0)	1 (12.5)
SKIN LESION	1 (10.0)	0 (0.0)	0 (0.0)

Serious Adverse Events and Deaths

	LDT600 15mg/kg N=10 n (%)	LDT600 25mg/kg N=5 n (%)	LDT600 600mg N=8 n (%)
Patients with SAE(s)	0 (0.0)	0 (0.0)	0 (0.0)
Death	0(0.0)	0(0.0)	0(0.0)

Other Relevant Findings

Not applicable

Date of Clinical Trial Report

27-Aug-2012

Date Inclusion on Novartis Clinical Trial Results Database

10-Sep-2012

Date of Latest Update