Clinical trial results:
An Open-label, Single-arm, Multicenter, Phase IV, 52-week Study to Evaluate the Efficacy and Safety of Telbivudine 600mg Tablets in Chinese Patients with Chronic Hepatitis B

Summary

EudraCT number	2016-001444-20
Trial protocol	Outside EU/EEA
Global end of trial date	16 September 2010

Results information

Result version number	v1 (current)
This version publication date	04 January 2017
First version publication date	04 January 2017

Trial information

Trial identification

Sponsor protocol code	CLDT600ACN03

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00781105
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 61324111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, +41 61324111,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 September 2010
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 September 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to evaluate the antiviral efficacy of telbivudine in terms of percentage of subjects achieving Hepatitis B virus (HBV) DNA <300 copies/millilitres (mL) at week 52.

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	01 August 2008
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	China: 2211
Worldwide total number of subjects	2211
EEA total number of subjects	0

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)	0
Adolescents (12-17 years)	26
Adults (18-64 years)	2183
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 48 centers in China.

Pre-assignment

Screening details:

A total of 2211 subjects were enrolled in the study.

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:

The study was open label study, hence no blinding was performed

Arms

Are arms mutually exclusive?	Yes
Arm title	Hepatitis B 'e' antigen (HBeAg) positive

Arm description:

Subjects who were HBeAg positive with chronic hepatitis B (CHB) were orally administered with telbivudine 600 milligrams (mg) tablets daily for a duration of 52 weeks. Dose modification was done for subjects who were unable to tolerate the treatment and had moderate to severe adverse reactions.

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

Dosage and administration details:

Subjects were orally administered with telbivudine 600 mg film coated tablets daily for a duration of 52 weeks.

Arm title	Hepatitis B 'e' antigen (HBeAg) negative

Arm description:

Subjects who were HBeAg negative with CHB were orally administered with telbivudine 600 mg tablets daily for a duration of 52 weeks. Dose modification was done for subjects who were unable to tolerate the treatment and had moderate to severe adverse reactions.

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

Dosage and administration details:

Subjects were orally administered with telbivudine 600 mg film coated tablets daily for a duration of 52 weeks.

Number of subjects in period 1[1]	Hepatitis B 'e' antigen (HBeAg) positive	Hepatitis B 'e' antigen (HBeAg) negative
Started	1752	406
Completed	1752	406

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The ITT population, 97.6% (2158 patients) received at least one dose of Telbivudine and had at least one post-baseline assessment of serum HBV DNA (ITT population).

Baseline characteristics

Reporting groups	
Reporting group title	Hepatitis B 'e' antigen (HBeAg) positive
Reporting group description:	
Subjects who were HBeAg positive with chronic hepatitis B (CHB) were orally administered with telbivudine 600 milligrams (mg) tablets daily for a duration of 52 weeks. Dose modification was done for subjects who were unable to tolerate the treatment and had moderate to severe adverse reactions.	
Reporting group title	Hepatitis B 'e' antigen (HBeAg) negative
Reporting group description:	
Subjects who were HBeAg negative with CHB were orally administered with telbivudine 600 mg tablets daily for a duration of 52 weeks. Dose modification was done for subjects who were unable to tolerate the treatment and had moderate to severe adverse reactions.	

Reporting group values	Hepatitis B 'e' antigen (HBeAg) positive	Hepatitis B 'e' antigen (HBeAg) negative	Total
Number of subjects	1752	406	2158
Age categorical			
Units: Subjects			
Adolescents (12-17 years)	25	1	26
Adults (18-64 years)	1726	404	2130
From 65-84 years	1	1	2
Age continuous			
Units: years			
arithmetic mean	30.2	38.2	
standard deviation	± 9	± 10.49	-
Gender categorical			
Units: Subjects			
Female	457	75	532
Male	1295	331	1626

End points

End points reporting groups

Reporting group title	Hepatitis B 'e' antigen (HBeAg) positive

Reporting group description:

Subjects who were HBeAg positive with chronic hepatitis B (CHB) were orally administered with telbivudine 600 milligrams (mg) tablets daily for a duration of 52 weeks. Dose modification was done for subjects who were unable to tolerate the treatment and had moderate to severe adverse reactions.

Reporting group title	Hepatitis B 'e' antigen (HBeAg) negative

Reporting group description:

Subjects who were HBeAg negative with CHB were orally administered with telbivudine 600 mg tablets daily for a duration of 52 weeks. Dose modification was done for subjects who were unable to tolerate the treatment and had moderate to severe adverse reactions.

Subject analysis set title	Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

All subjects who received at least one dose of telbivudine 600 mg/day tablets and had at least one evaluable post-baseline safety assessment.

Primary: Percentage of subjects achieving HBV DNA <300 copies/mL at Week 52

End point title	Percentage of subjects achieving HBV DNA <300 copies/mL at Week 52[1]

End point description:

Undetectable serum HBV DNA was defined as HBV DNA <300 copies/mL determined by COBAS Taqman HBV assay. The assay utilized polymerase chain reaction (PCR) methods and automated sample readout technologies. The analysis was performed on Intent-to-treat (ITT) population defined as all subjects who received at least one dose of telbivudine 600 mg tablets and had at least one post-baseline assessment of serum HBV DNA.

End point type	Primary

End point timeframe:

From Baseline to Week 52

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: Only descriptive summary statistics was planned for this outcome measure.

End point values	Hepatitis B 'e' antigen (HBeAg) positive	Hepatitis B 'e' antigen (HBeAg) negative		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1749	405		
Units: Percentage				
number (confidence interval 95%)	54.3 (51.79 to 56.74)	86.5 (82.5 to 89.82)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects achieving HBV DNA <300 copies/mL at Week 24

End point title	Percentage of subjects achieving HBV DNA <300 copies/mL at Week 24

End point description:

Undetectable serum HBV DNA was defined as HBV DNA <300 copies/mL determined by COBAS Taqman HBV assay. The assay utilized PCR methods and automated sample readout technologies. The analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

From Baseline to Week 24

End point values	Hepatitis B 'e' antigen (HBeAg) positive	Hepatitis B 'e' antigen (HBeAg) negative		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1749	405		
Units: Percentage				
number (confidence interval 95%)	36.2 (33.92 to 38.53)	82.6 (78.47 to 86.18)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean reduction in HBV DNA from baseline at Week 12, 24, 36 and 52

End point title	Mean reduction in HBV DNA from baseline at Week 12, 24, 36 and 52

End point description:

HBeAg loss was defined as serum HBeAg undetectable in a subject and HBeAg seroconversion was defined as serum HBeAg undetectable and anti-HBe detectable with HBeAg detectable at baseline. In HBeAg positive subjects, loss of detectable serum HBsAg (HBeAg loss) with gain of detectable anti-HBe antibody (HBeAg seroconversion), usually indicated a subject's transition to a state of substantially lower HBV replication. HBV serologic markers were assessed using standard commercially-available assays. This analysis was performed on ITT population for only those subjects who were HBeAg positive at baseline. The analysis was done using a last observation carried forward approach.

End point type	Secondary

End point timeframe:

At Baseline, Week 12, Week 24, Week 36 and Week 52

End point values	Hepatitis B 'e' antigen (HBeAg) positive	Hepatitis B 'e' antigen (HBeAg) negative		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1749	405		
Units: Log^10 copies/ mL				
arithmetic mean (standard deviation)				
Week 12 (n = 1726, 400)	-4.17 (± 1.25)	-3.57 (± 1.344)		
Week 24 (n = 1741, 402)	-4.91 (± 1.449)	-4.2 (± 1.351)		

Week 36 (n = 1742, 402)	-5.13 (± 1.605)	-4.27 (± 1.477)		
Week 52 (n = 1744, 402)	-5.07 (± 1.917)	-4.2 (± 1.663)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of HBeAg positive subjects with HBeAg loss and seroconversion at Week 52

End point title	Percentage of HBeAg positive subjects with HBeAg loss and seroconversion at Week 52[2]

End point description:

HBeAg loss was defined as serum HBeAg undetectable in a subject with HBeAg detectable at baseline. HBeAg seroconversion was defined as serum HBeAg undetectable and anti-HBe detectable in subjects with HBeAg detectable at baseline. In HBeAg positive subjects, loss of detectable serum HBsAg (HBeAg loss) with gain of detectable anti-HBe antibody (HBeAg seroconversion), usually indicated a subject's transition to a state of substantially lower HBV replication. HBV serologic markers were assessed using standard commercially-available assays at week 52 from baseline. This analysis was performed on ITT population for only those subjects who were HBeAg positive at baseline. The analysis was done using a last observation carried forward approach.

End point type	Secondary

End point timeframe:

From Baseline to Week 52

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Percentage of subjects with HBeAg loss/ seroconversion at week 52 was evaluated only for those subjects who were HBeAg positive at baseline.

End point values	Hepatitis B 'e' antigen (HBeAg) positive			
Subject group type	Reporting group			
Number of subjects analysed	1752			
Units: Percentage				
number (confidence interval 95%)				
HBeAg loss	22.7 (20.78 to 24.76)			
HBeAg seroconversion	19.6 (17.74 to 21.52)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with Alanine aminotransferase (ALT) normalization at Week 24 and Week 52

End point title	Percentage of subjects with Alanine aminotransferase (ALT) normalization at Week 24 and Week 52

End point description:

ALT normalization was defined as ALT level returning to below upper limit of normal (ULN). ALT levels were determined from serum samples at study site using standard methods. The analysis was performed on ITT population. The analysis was done using a last observation carried forward approach.

End point type	Secondary

End point timeframe:

At Baseline, Week 24 and Week 52

End point values	Hepatitis B 'e' antigen (HBeAg) positive	Hepatitis B 'e' antigen (HBeAg) negative		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1670	356		
Units: Percentage				
number (confidence interval 95%)				
Week 24 (n = 1670, 356)	73.8 (71.64 to 75.93)	78.2 (73.58 to 82.44)		
Week 52 (n = 1670, 356)	81.3 (79.35 to 83.16)	78 (73.28 to 82.18)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with HBsAg loss and seroconversion at Week 52

End point title	Percentage of subjects with HBsAg loss and seroconversion at Week 52

End point description:

Hepatitis B surface antigen (HBsAg) loss was defined as serum HBsAg undetectable in a subject with HBsAg detectable at baseline. HBsAg seroconversion was defined as serum HBsAg undetectable and HB surface antibody (anti-HBs) detectable in a patient with HBsAg detectable at baseline. Serum HBsAg and seroconversion was assessed using standard commercially-available enzyme immunoassays. This analysis was performed on ITT population. The analysis was done using a last observation carried forward approach.

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Hepatitis B 'e' antigen (HBeAg) positive	Hepatitis B 'e' antigen (HBeAg) negative		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1752	406		
Units: Percentage				
number (confidence interval 95%)				

HBsAg loss	0.5 (0.2 to 0.9)	0.2 (0.01 to 1.37)		
HBsAg seroconversion	0.2 (0.06 to 0.59)	0.2 (0.01 to 1.37)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with virologic breakthrough at Week 52

End point title	Percentage of subjects with virologic breakthrough at Week 52

End point description:

Virologic breakthrough was defined as HBV DNA ≥1 log 10 copies/mL from nadir on two consecutive visits or at last on-treatment visit for subjects on treatment who achieved HBV DNA ≥1 log 10 copies/mL (10-fold) reduction from baseline on two consecutive visits. Subjects who had not achieved a reduction from baseline in HBV DNA but did exhibit an increase ≥1 log 10 were not indicative of virologic breakthrough but could be a result of primary non-response instead. This analysis was performed on ITT population and included patients who were under treatment at the week 52 visit and who were not previously treated with immune modulators or nucleos(t)ides. The analysis was done using a last observation carried forward approach.

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Hepatitis B 'e' antigen (HBeAg) positive	Hepatitis B 'e' antigen (HBeAg) negative		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1752	406		
Units: Percentage				
number (not applicable)	6.8	5.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with adverse events (AEs), serious adverse events (SAEs), AEs and drug related AEs leading to discontinuation, study medication interruption (not discontinuation due to AE) and who died

End point title	Number of subjects with adverse events (AEs), serious adverse events (SAEs), AEs and drug related AEs leading to discontinuation, study medication interruption (not discontinuation due to AE) and who died

End point description:

AEs are defined as any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome or disease which either occurs during study, having been absent at baseline, or, if present at baseline, appears to worsen. Serious adverse events are any untoward medical occurrences that result in death, are life threatening, require (or prolong) hospitalization, cause persistent or significant disability/incapacity, result in congenital anomalies or birth defects, or are other

conditions which in judgment of investigators represent significant hazards. Adverse events of special interest (AESI) depended on severity and relationship to telbivudine. The analysis was done on safety population.

End point type	Secondary

End point timeframe:

From Baseline to 30 days after last dose of study treatment

End point values	Safety population			
Subject group type	Subject analysis set			
Number of subjects analysed	2206			
Units: Subjects				
AEs	246			
AESIs	131			
SAEs	28			
AEs leading to discontinuation	27			
Drug related AEs leading to discontinuation	24			
Study medication interruption	6			
Death	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with Grade 3 or 4 laboratory abnormalities

End point title	Number of subjects with Grade 3 or 4 laboratory abnormalities

End point description:

Laboratory abnormalities were analyzed by shift tables and each subject was counted only once. New onset grade 3/4 abnormalities of the laboratory parameters from baseline to week 52 were analyzed for hematology, serum biochemistry and urinalysis. “New onset” was defined as laboratory assessments with increased toxicity grades compared with baseline values. Limits for GRADE 3 lab abnormalities were: Hematology; absolute neutrophil count (500-749 /millimeter cube (mm^3)), hemoglobin (6.4 - < 8 grams (g)/ deciliter (dl)), platelet count (20,000-49,999/mm^3), prothrombin time (1.5-3.0 ULN), White Blood Cell (1.0 - <5.0*10^9/ Litres (L)); Clinical Biochemistry; ALT (3- 10*baseline) ,AST (3-10*baseline), albumin (2.0-2.5 g/L), amylase (>3 - 10*ULN), creatine kinase (>7 - 10*ULN), creatinine (>3 - 6.0*ULN), total bilirubin (>5 -10*ULN) and urinalysis(protein: 2- 3.5 g loss per day OR > =1% OR > = 10 g/L).

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Safety population			
Subject group type	Subject analysis set			
Number of subjects analysed	2206			
Units: Subjects				
Absolute neutrophil Count	2			
Hemoglobin	1			
Platelet count	12			
Prothrombin Time	7			
White Blood Cell	1			
ALT	25			
AST	19			
Albumin	0			
Amylase	0			
Creatine Kinase	69			
Creatinine	0			
Total bilirubin	0			
Urinalysis (Protein)	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with clinically significant changes in vital signs

End point title	Number of subjects with clinically significant changes in vital signs

End point description:

Subjects with vital signs namely blood pressure (BP): systolic blood pressure (SBP) millimeter of mercury (mmHg): result <90, result >180, or change > 20; diastolic BP (DBP) (mmHg): result <50, result >105, or change>15; heart rate (bpm): result<50, result >120, or change > 15 outside the defined normal range were graded as clinically significant vital signs. The analysis was performed on the safety population.

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Safety population			
Subject group type	Subject analysis set			
Number of subjects analysed	2206			
Units: Subjects				
Low SBP	1			
High DBP	1			
Low heart rate	1			
High heart rate	1			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious Adverse Events are monitored from date of First Subject First Visit (FSFV) until Last Subject Last Visit (LSLV). All other adverse events are monitored from First Subject First Treatment until LSLV.

Adverse event reporting additional description:

AE additional description

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.0

Reporting groups

Reporting group title	HBeAg negative

Reporting group description:

Subjects who were HBeAg negative with CHB were orally administered with telbivudine 600 mg tablets daily for a duration of 52 weeks. Dose modification was done for subjects who were unable to tolerate the treatment and had moderate to severe adverse reactions.

Reporting group title	HBeAg positive

Reporting group description:

Subjects who were HBeAg positive with CHB were orally administered with telbivudine 600 mg tablets daily for a duration of 52 weeks. Dose modification was done for subjects who were unable to tolerate the treatment and had moderate to severe adverse reactions

Serious adverse events	HBeAg negative	HBeAg positive	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 420 (1.19%)	23 / 1786 (1.29%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 420 (0.24%)	5 / 1786 (0.28%)	
occurrences causally related to treatment / all	1 / 1	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatic neoplasm malignant			
subjects affected / exposed	0 / 420 (0.00%)	1 / 1786 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Rectal cancer			

subjects affected / exposed	1 / 420 (0.24%)	0 / 1786 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Teratoma			
subjects affected / exposed	0 / 420 (0.00%)	1 / 1786 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	0 / 420 (0.00%)	1 / 1786 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Heart block congenital			
subjects affected / exposed	1 / 420 (0.24%)	0 / 1786 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Internal fixation of fracture			
subjects affected / exposed	0 / 420 (0.00%)	1 / 1786 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 420 (0.00%)	1 / 1786 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 420 (0.00%)	1 / 1786 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucous membrane disorder			

subjects affected / exposed	0 / 420 (0.00%)	1 / 1786 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Reflux gastritis			
subjects affected / exposed	0 / 420 (0.00%)	1 / 1786 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	0 / 420 (0.00%)	1 / 1786 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	0 / 420 (0.00%)	2 / 1786 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	1 / 420 (0.24%)	0 / 1786 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	1 / 420 (0.24%)	3 / 1786 (0.17%)	
occurrences causally related to treatment / all	1 / 1	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myopathy			
subjects affected / exposed	0 / 420 (0.00%)	5 / 1786 (0.28%)	
occurrences causally related to treatment / all	0 / 0	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myositis			

subjects affected / exposed	0 / 420 (0.00%)	1 / 1786 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 420 (0.00%)	2 / 1786 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis B			
subjects affected / exposed	2 / 420 (0.48%)	2 / 1786 (0.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngitis			
subjects affected / exposed	0 / 420 (0.00%)	1 / 1786 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 420 (0.00%)	1 / 1786 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	HBeAg negative	HBeAg positive	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 420 (4.76%)	74 / 1786 (4.14%)	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	20 / 420 (4.76%)	74 / 1786 (4.14%)	
occurrences (all)	20	79	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 March 2009	Part of the inclusion criteria had been changed as following: *Central lab detected serum HBV DNA level >=1^5 copies/mL for HBeAg positive subjects; >= 1^4 copies/mL for HBeAg negative subjects at the screening visit *Elevated serum ALT >=1.3^ULN and <10^ULN at screening visit (non- HBV factors' impact on ALT was excluded, such as drug or alcohol). Part of the exclusion criteria had been changed as following: *Subject had a history of or clinical signs/symptoms of hepatic decompensation such as evidenced by ascites, esophageal variceal bleeding, hepatic encephalopathy, or spontaneous bacterial peritonitis; or Child- Pugh Grade B or C. *Subject had any of the following laboratory values during screening period: a.Hemoglobin <11 g/dL for men or <10 g/dL for women b. Total WBC <3,500/mm^3 c. Absolute neutrophil count (ANC) <1,500/mm^3 d. Platelet count <80,000/mm^3 e. Serum albumin <3.5 g/dL f. Total bilirubin ≥ 2.0mg/dL g. Serum creatinine ≥ 1.5mg/dL h. Serum creatine kinase ≥ 5*ULN i. PT prolongation by ≥ 3sec (based on the ULN of the reference value) or PTA ≤60% j. Serum amylases ≥ 1.5* ULN. Following changes to Appendix 1 were made: 1. All drugs other than protocol defined anti-HBV medications: lamivudine,adefovir, entecavir, tenofovir, emtricitabine (FTC), lobucavir, etc. 2. Any type of immunomodulators: interferons (PEG-, or alpha-, beta-,gamma-interferon,etc), thymosin, IL-12, or other recognized systemic immunomodulators 3. Liver protectors and/or enzyme reducers, including but were not limited to (e.g.herbal medications, Diammonium glycyrrhizinate, shizandrin A, bifendate, sedum sarmentosum beg, potassium and magnesium apsparate, reduced glutathione, oxymatrine, etc.). 4. Prolonged use of systemic acyclovir,famciclovir or ganciclovir defined as episodic treatment with these agents for periods exceeding 10 days every 3 months, or chronic suppressive therapy.
11 March 2009	Continued from above: 5. Systemic corticosteroids (topical and inhaled corticosteroids were permitted). 6. Hepatotoxic drugs (e.g., dapsone, erythromycin, fluconazole, ketoconazole, rifampin or anti-tuberculosis drugs, toxic doses of acetaminophen), as well as herbal medications known to cause hepatotoxicity (e.g., St. John's Wart, milk thistle, Kava,Jin Bu Huan, Yuzhitang, germander, chaparral, shark cartilage, mistletoe, slim 10,Lipokinetix, etc.). 7. Nephrotoxic drugs (e.g., non-steroidal anti-inflammatory use, aminoglycosides, amphotericin B, foscarnet, etc.). 8. Alcohol or illicit drug abuse. For the purposes of the present study, alcohol abuse was arbitrarily defined as frequent consumption of alcoholic beverages with an average daily intake of more than 40g of ethanol. 9. Drugs associated with myopathy, including corticosteroids, chloroquine, hydroxychloroquine, certain HMGCoA reductase inhibitors, fibric acid derivatives, penicilamine, zidovudine, cyclosporine, erythromycin, niacin, and/or azole antifungals.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported