



Clinical trial results:

Evaluation of the Pharmacokinetics, Safety, Tolerability and Efficacy of Entecavir (ETV) in Pediatric Subjects with Chronic Hepatitis B Virus (HBV) Infection who are HBeAg-Positive

Summary

EudraCT number	2005-005816-26
Trial protocol	GB BE Outside EU/EEA
Global end of trial date	04 September 2017

Results information

Result version number	v1 (current)
This version publication date	16 March 2018
First version publication date	16 March 2018

Trial information

Trial identification

Sponsor protocol code	AI463-028
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussée de la Hulpe 185, Brussels, Belgium, 1170
Public contact	EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, clinical.trials@bms.com
Scientific contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-000339-PIP02-09
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	04 September 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	04 September 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of study AI463028 was (1) to evaluate the pharmacokinetic (PK) profile of entecavir (ETV) in children and adolescents in order to identify doses that produce drug exposures comparable to those observed in adults receiving the currently approved 0.5 mg and 1.0 doses; and (2) to describe the safety, tolerability and preliminary efficacy of ETV in pediatric subjects ≥ 2 to ≤ 18 years of age who had chronic hepatitis B virus (HBV) infection and were hepatitis B e antigen (HBeAg)-positive.

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 Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 June 2007
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	Argentina: 3
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Brazil: 5
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Korea, Republic of: 18
Country: Number of subjects enrolled	Taiwan: 5
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	United States: 25
Worldwide total number of subjects	64
EEA total number of subjects	6

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)	39
Adolescents (12-17 years)	25
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study started June 2007, currently ongoing. Cohort 1: age ≥ 2 to ≤ 6 years; Cohort 2: >6 to ≤ 12 years; Cohort 3: age >12 to ≤ 18 years. Groups A and B: lamivudine-naive and experienced participants, respectively. Nucleoside/tide analog - treatment-experienced participants (Group C) added September 2011 via country-specific amendment to protocol.

Pre-assignment

Screening details:

64 enrolled. 48 treated. Participants received a minimum of 48 weeks study drug but depending on response to drug, could remain on treatment for up to a total of 120 weeks. Participants were to receive post dosing follow up after last dose, for a total of 5 years on-study (on and off study drug).

Period 1

Period 1 title	Enrolled
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Lamivudine (LVD)-naive (Group A)

Arm description:

Participants with less than ($<$) 1 week of prior LVD therapy and with no LVD therapy within 24 weeks prior to enrollment were included in Group A. Prior to Pharmacokinetic (PK) assessment, Cohort 1 (age ≥ 2 years to ≤ 6 years) and Cohort 2 (>6 years to ≤ 12 years) received ETV oral solution, 0.015 mg/kg up to 0.5 mg, once a day (QD) and Cohort 3 (age >12 years to ≤ 18 years) received ETV oral solution, 0.015 mg/kg up to 0.5 mg, or ETV tablets, 0.5 mg, QD. Following PK analysis, those who met the specified dosing requirements (at least 0.5 mg/day) and could tolerate swallowing ETV tablets were allowed to choose either formulation. Entecavir (ETV) was administered for a maximum of 120 weeks.

Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	Lamivudine (LVD)-experienced (Group B)

Arm description:

Participants with greater than ($>$) 12 weeks of prior LVD therapy were included in Group B. Prior to PK assessment, Cohort 1 (age ≥ 2 years to ≤ 6 years) and Cohort 2 (>6 years to ≤ 12 years) received ETV oral solution, 0.030 mg/kg up to 1.0 mg, QD and Cohort 3 (age >12 years to ≤ 18 years) received ETV oral solution, 0.030 mg/kg up to 1.0 mg, or ETV tablets, 1.0 mg QD. Following PK analysis, those who met the specified dosing requirements (at least 1.0 mg/day) and could tolerate swallowing ETV tablets were allowed to choose either formulation. Entecavir (ETV) was administered for a maximum of 120 weeks.

Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	Nucleoside/tide analog (NA) - experienced (Group C)

Arm description:

Participants who failed previous treatment with any non-ETV nucleoside/tide analog (NA) were included in Group C, starting in 2011. PK assessment was optional to participants in Group C. All participants received ETV oral solution, 0.030 mg/kg up to 1.0 mg, or ETV tablets, 1.0 mg, QD. Participants who met the specified dosing requirements (at least 1.0 mg/day for NA-experienced participants) and could tolerate swallowing ETV tablets were allowed to choose either formulation. ETV was administered for a maximum of 120 weeks.

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	Lamivudine (LVD)-naïve (Group A)	Lamivudine (LVD)-experienced (Group B)	Nucleoside/tide analog (NA) - experienced (Group C)
Started	35	21	8
Completed	24	19	5
Not completed	11	2	3
Consent withdrawn by subject	-	-	1
Lost to follow-up	-	-	1
No longer met criteria	11	2	1

Period 2

Period 2 title	Treatment
Is this the baseline period?	Yes ^[1]
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Lamivudine (LVD)-naïve (Group A)

Arm description:

Participants with less than (<) 1 week of prior LVD therapy and with no LVD therapy within 24 weeks prior to enrollment were included in Group A. Prior to Pharmacokinetic (PK) assessment, Cohort 1 (age ≥ 2 years to ≤ 6 years) and Cohort 2 (>6 years to ≤ 12 years) received ETV oral solution, 0.015 mg/kg up to 0.5 mg, once a day (QD) and Cohort 3 (age >12 years to ≤ 18 years) received ETV oral solution, 0.015 mg/kg up to 0.5 mg, or ETV tablets, 0.5 mg, QD. Following PK analysis, those who met the specified dosing requirements (at least 0.5 mg/day) and could tolerate swallowing ETV tablets were allowed to choose either formulation. Entecavir (ETV) was administered for a maximum of 120 weeks.

Arm type	Experimental
Investigational medicinal product name	Entecavir
Investigational medicinal product code	
Other name	BMS-200475
Pharmaceutical forms	Tablet, Oral solution
Routes of administration	Oral use

Dosage and administration details:

Entecavir (ETV) 0.015 mg/kg up to 0.5 mg, once a day (QD)

Arm title	Lamivudine (LVD)-experienced (Group B)
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Arm description:

Participants with greater than (>) 12 weeks of prior LVD therapy were included in Group B. Prior to PK assessment, Cohort 1 (age ≥ 2 years to ≤ 6 years) and Cohort 2 (>6 years to ≤ 12 years) received ETV oral solution, 0.030 mg/kg up to 1.0 mg, QD and Cohort 3 (age >12 years to ≤ 18 years) received ETV oral solution, 0.030 mg/kg up to 1.0 mg, or ETV tablets, 1.0 mg QD. Following PK analysis, those who met the specified dosing requirements (at least 1.0 mg/day) and could tolerate swallowing ETV tablets were allowed to choose either formulation. Entecavir (ETV) was administered for a maximum of 120 weeks.

Arm type	Experimental
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Investigational medicinal product name	Entecavir
Investigational medicinal product code	
Other name	BMS-200475
Pharmaceutical forms	Oral solution, Tablet
Routes of administration	Oral use
Dosage and administration details:	
Entecavir (ETV) 0.030 mg/kg up to 1.0 mg, once a day (QD)	
Arm title	Nucleoside/tide analog (NA) - experienced (Group C)

Arm description:

Participants who failed previous treatment with any non-ETV nucleoside/tide analog (NA) were included in Group C, starting in 2011. PK assessment was optional to participants in Group C. All participants received ETV oral solution, 0.030 mg/kg up to 1.0 mg, or ETV tablets, 1.0 mg, QD. Participants who met the specified dosing requirements (at least 1.0 mg/day for NA-experienced participants) and could tolerate swallowing ETV tablets were allowed to choose either formulation. ETV was administered for a maximum of 120 weeks.

Arm type	Experimental
Investigational medicinal product name	Entecavir
Investigational medicinal product code	
Other name	BMS-200475
Pharmaceutical forms	Oral solution, Tablet
Routes of administration	Oral use

Dosage and administration details:

Entecavir (ETV) 0.030 mg/kg up to 1.0 mg, once a day (QD)

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Baseline characteristics were calculated only for treated subjects (Period 2).

Number of subjects in period 2 ^[2]	Lamivudine (LVD)-naive (Group A)	Lamivudine (LVD)-experienced (Group B)	Nucleoside/tide analog (NA) - experienced (Group C)
Started	24	19	5
Completed	22	19	5
Not completed	2	0	0
Consent withdrawn by subject	1	-	-
Lost to follow-up	1	-	-

Notes:

[2] - 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: 64 enrolled. 48 treated. Participants received a minimum of 48 weeks study drug but depending on response to drug, could remain on treatment for up to a total of 120 weeks. Participants were to receive post dosing follow up after last dose, for a total of 5 years on-study (on and off study drug).

Period 3

Period 3 title	Post-Dosing Follow Up
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
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Arm title	Lamivudine (LVD)-naive (Group A)
Arm description:	
Participants with less than (<) 1 week of prior LVD therapy and with no LVD therapy within 24 weeks prior to enrollment were included in Group A. Prior to Pharmacokinetic (PK) assessment, Cohort 1 (age ≥ 2 years to ≤ 6 years) and Cohort 2 (>6 years to ≤ 12 years) received ETV oral solution, 0.015 mg/kg up to 0.5 mg, once a day (QD) and Cohort 3 (age >12 years to ≤18 years) received ETV oral solution, 0.015 mg/kg up to 0.5 mg, or ETV tablets, 0.5 mg, QD. Following PK analysis, those who met the specified dosing requirements (at least 0.5 mg/day) and could tolerate swallowing ETV tablets were allowed to choose either formulation. Entecavir (ETV) was administered for a maximum of 120 weeks.	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	Lamivudine (LVD)-experienced (Group B)
Arm description:	
Participants with greater than (>) 12 weeks of prior LVD therapy were included in Group B. Prior to PK assessment, Cohort 1 (age ≥ 2 years to ≤ 6 years) and Cohort 2 (> 6 years to ≤ 12 years) received ETV oral solution, 0.030 mg/kg up to 1.0 mg, QD and Cohort 3 (age >12 years to ≤18 years) received ETV oral solution, 0.030 mg/kg up to 1.0 mg, or ETV tablets, 1.0 mg QD. Following PK analysis, those who met the specified dosing requirements (at least 1.0 mg/day) and could tolerate swallowing ETV tablets were allowed to choose either formulation. Entecavir (ETV) was administered for a maximum of 120 weeks.	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	Nucleoside/tide analog (NA) - experienced (Group C)
Arm description:	
Participants who failed previous treatment with any non-ETV nucleoside/tide analog (NA) were included in Group C, starting in 2011. PK assessment was optional to participants in Group C. All participants received ETV oral solution, 0.030 mg/kg up to 1.0 mg, or ETV tablets, 1.0 mg, QD. Participants who met the specified dosing requirements (at least 1.0 mg/day for NA-experienced participants) and could tolerate swallowing ETV tablets were allowed to choose either formulation. ETV was administered for a maximum of 120 weeks.	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 3 ^[3]	Lamivudine (LVD)-naive (Group A)	Lamivudine (LVD)-experienced (Group B)	Nucleoside/tide analog (NA) - experienced (Group C)
Started	22	18	5
Completed	20	15	3
Not completed	2	3	2
Consent withdrawn by subject	-	3	2
Lost to follow-up	2	-	-

Notes:

[3] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: One subject in Group B did not enter the follow-up period.

Baseline characteristics

Reporting groups

Reporting group title	Lamivudine (LVD)-naive (Group A)
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Reporting group description:

Participants with less than (<) 1 week of prior LVD therapy and with no LVD therapy within 24 weeks prior to enrollment were included in Group A. Prior to Pharmacokinetic (PK) assessment, Cohort 1 (age ≥ 2 years to ≤ 6 years) and Cohort 2 (>6 years to ≤ 12 years) received ETV oral solution, 0.015 mg/kg up to 0.5 mg, once a day (QD) and Cohort 3 (age >12 years to ≤ 18 years) received ETV oral solution, 0.015 mg/kg up to 0.5 mg, or ETV tablets, 0.5 mg, QD. Following PK analysis, those who met the specified dosing requirements (at least 0.5 mg/day) and could tolerate swallowing ETV tablets were allowed to choose either formulation. Entecavir (ETV) was administered for a maximum of 120 weeks.

Reporting group title	Lamivudine (LVD)-experienced (Group B)
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Reporting group description:

Participants with greater than (>) 12 weeks of prior LVD therapy were included in Group B. Prior to PK assessment, Cohort 1 (age ≥ 2 years to ≤ 6 years) and Cohort 2 (> 6 years to ≤ 12 years) received ETV oral solution, 0.030 mg/kg up to 1.0 mg, QD and Cohort 3 (age >12 years to ≤ 18 years) received ETV oral solution, 0.030 mg/kg up to 1.0 mg, or ETV tablets, 1.0 mg QD. Following PK analysis, those who met the specified dosing requirements (at least 1.0 mg/day) and could tolerate swallowing ETV tablets were allowed to choose either formulation. Entecavir (ETV) was administered for a maximum of 120 weeks.

Reporting group title	Nucleoside/tide analog (NA) - experienced (Group C)
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Reporting group description:

Participants who failed previous treatment with any non-ETV nucleoside/tide analog (NA) were included in Group C, starting in 2011. PK assessment was optional to participants in Group C. All participants received ETV oral solution, 0.030 mg/kg up to 1.0 mg, or ETV tablets, 1.0 mg, QD. Participants who met the specified dosing requirements (at least 1.0 mg/day for NA-experienced participants) and could tolerate swallowing ETV tablets were allowed to choose either formulation. ETV was administered for a maximum of 120 weeks.

Reporting group values	Lamivudine (LVD)-naive (Group A)	Lamivudine (LVD)-experienced (Group B)	Nucleoside/tide analog (NA) - experienced (Group C)
Number of subjects	24	19	5
Age, Customized			
Units: Subjects			
≥ 2 years to ≤ 6 years	7	3	2
>6 years to ≤ 12 years	9	7	2
>12 years to ≤ 18 years	8	9	1
Age Continuous			
Units: years			
arithmetic mean	9.2	11.0	8.8
standard deviation	± 5.41	± 4.42	± 5.02
Gender, Male/Female			
Units: Subjects			
Female	14	7	2
Male	10	12	3
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	17	10	5
Native Hawaiian or Other Pacific Islander	0	1	0
Black or African American	0	2	0

White	5	6	0
More than one race	0	0	0
Unknown or Not Reported	2	0	0
Region of Enrollment			
Units: Subjects			
United States	10	5	1
Taiwan	3	0	0
Canada	1	0	0
Argentina	3	0	0
Belgium	1	1	0
Brazil	1	3	0
United Kingdom	2	1	0
Korea, Republic of	3	9	4
Alanine Aminotransferase (ALT)			
The normal range for serum ALT as established by the study's central laboratory was 5 - 45 units per liter (U/L). The inclusion criteria for Groups A and B was $\geq 2 \times \text{ULN}$ to $\leq 10 \times \text{ULN}$, while only the upper range applied to Group C ($\leq 10 \times \text{ULN}$).			
Units: U/L			
arithmetic mean	142.8	125.7	44.6
standard deviation	± 85.18	± 67.96	± 22.96
Hepatitis B virus (HBV) deoxyribonucleic acid (DNA)			
Hepatitis B virus DNA by polymerase chain reaction (PCR) was measured using the Roche COBAS TaqMan - high pure system (HPS) assay and was reported in international units per milliliter (IU/mL).			
Units: log ₁₀ IU/mL			
arithmetic mean	7.92	7.74	7.96
standard deviation	± 0.864	± 0.856	± 0.238

Reporting group values	Total		
Number of subjects	48		
Age, Customized			
Units: Subjects			
≥ 2 years to ≤ 6 years	12		
>6 years to ≤ 12 years	18		
>12 years to ≤ 18 years	18		
Age Continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender, Male/Female			
Units: Subjects			
Female	23		
Male	25		
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0		
Asian	32		
Native Hawaiian or Other Pacific Islander	1		
Black or African American	2		
White	11		
More than one race	0		
Unknown or Not Reported	2		

Region of Enrollment			
Units: Subjects			
United States	16		
Taiwan	3		
Canada	1		
Argentina	3		
Belgium	2		
Brazil	4		
United Kingdom	3		
Korea, Republic of	16		
Alanine Aminotransferase (ALT)			
The normal range for serum ALT as established by the study's central laboratory was 5 - 45 units per liter (U/L). The inclusion criteria for Groups A and B was $\geq 2 \times \text{ULN}$ to $\leq 10 \times \text{ULN}$, while only the upper range applied to Group C ($\leq 10 \times \text{ULN}$).			
Units: U/L			
arithmetic mean			
standard deviation	-		
Hepatitis B virus (HBV) deoxyribonucleic acid (DNA)			
Hepatitis B virus DNA by polymerase chain reaction (PCR) was measured using the Roche COBAS TaqMan - high pure system (HPS) assay and was reported in international units per milliliter (IU/mL).			
Units: log ₁₀ IU/mL			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Lamivudine (LVD)-naïve (Group A)
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Reporting group description:

Participants with less than (<) 1 week of prior LVD therapy and with no LVD therapy within 24 weeks prior to enrollment were included in Group A. Prior to Pharmacokinetic (PK) assessment, Cohort 1 (age ≥ 2 years to ≤ 6 years) and Cohort 2 (>6 years to ≤ 12 years) received ETV oral solution, 0.015 mg/kg up to 0.5 mg, once a day (QD) and Cohort 3 (age >12 years to ≤ 18 years) received ETV oral solution, 0.015 mg/kg up to 0.5 mg, or ETV tablets, 0.5 mg, QD. Following PK analysis, those who met the specified dosing requirements (at least 0.5 mg/day) and could tolerate swallowing ETV tablets were allowed to choose either formulation. Entecavir (ETV) was administered for a maximum of 120 weeks.

Reporting group title	Lamivudine (LVD)-experienced (Group B)
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Reporting group description:

Participants with greater than (>) 12 weeks of prior LVD therapy were included in Group B. Prior to PK assessment, Cohort 1 (age ≥ 2 years to ≤ 6 years) and Cohort 2 (> 6 years to ≤ 12 years) received ETV oral solution, 0.030 mg/kg up to 1.0 mg, QD and Cohort 3 (age >12 years to ≤ 18 years) received ETV oral solution, 0.030 mg/kg up to 1.0 mg, or ETV tablets, 1.0 mg QD. Following PK analysis, those who met the specified dosing requirements (at least 1.0 mg/day) and could tolerate swallowing ETV tablets were allowed to choose either formulation. Entecavir (ETV) was administered for a maximum of 120 weeks.

Reporting group title	Nucleoside/tide analog (NA) - experienced (Group C)
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Reporting group description:

Participants who failed previous treatment with any non-ETV nucleoside/tide analog (NA) were included in Group C, starting in 2011. PK assessment was optional to participants in Group C. All participants received ETV oral solution, 0.030 mg/kg up to 1.0 mg, or ETV tablets, 1.0 mg, QD. Participants who met the specified dosing requirements (at least 1.0 mg/day for NA-experienced participants) and could tolerate swallowing ETV tablets were allowed to choose either formulation. ETV was administered for a maximum of 120 weeks.

Reporting group title	Lamivudine (LVD)-naïve (Group A)
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Reporting group description:

Participants with less than (<) 1 week of prior LVD therapy and with no LVD therapy within 24 weeks prior to enrollment were included in Group A. Prior to Pharmacokinetic (PK) assessment, Cohort 1 (age ≥ 2 years to ≤ 6 years) and Cohort 2 (>6 years to ≤ 12 years) received ETV oral solution, 0.015 mg/kg up to 0.5 mg, once a day (QD) and Cohort 3 (age >12 years to ≤ 18 years) received ETV oral solution, 0.015 mg/kg up to 0.5 mg, or ETV tablets, 0.5 mg, QD. Following PK analysis, those who met the specified dosing requirements (at least 0.5 mg/day) and could tolerate swallowing ETV tablets were allowed to choose either formulation. Entecavir (ETV) was administered for a maximum of 120 weeks.

Reporting group title	Lamivudine (LVD)-experienced (Group B)
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Reporting group description:

Participants with greater than (>) 12 weeks of prior LVD therapy were included in Group B. Prior to PK assessment, Cohort 1 (age ≥ 2 years to ≤ 6 years) and Cohort 2 (> 6 years to ≤ 12 years) received ETV oral solution, 0.030 mg/kg up to 1.0 mg, QD and Cohort 3 (age >12 years to ≤ 18 years) received ETV oral solution, 0.030 mg/kg up to 1.0 mg, or ETV tablets, 1.0 mg QD. Following PK analysis, those who met the specified dosing requirements (at least 1.0 mg/day) and could tolerate swallowing ETV tablets were allowed to choose either formulation. Entecavir (ETV) was administered for a maximum of 120 weeks.

Reporting group title	Nucleoside/tide analog (NA) - experienced (Group C)
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Reporting group description:

Participants who failed previous treatment with any non-ETV nucleoside/tide analog (NA) were included in Group C, starting in 2011. PK assessment was optional to participants in Group C. All participants received ETV oral solution, 0.030 mg/kg up to 1.0 mg, or ETV tablets, 1.0 mg, QD. Participants who met the specified dosing requirements (at least 1.0 mg/day for NA-experienced participants) and could tolerate swallowing ETV tablets were allowed to choose either formulation. ETV was administered for a maximum of 120 weeks.

Reporting group title	Lamivudine (LVD)-naïve (Group A)
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Reporting group description:

Participants with less than (<) 1 week of prior LVD therapy and with no LVD therapy within 24 weeks prior to enrollment were included in Group A. Prior to Pharmacokinetic (PK) assessment, Cohort 1 (age ≥ 2 years to ≤ 6 years) and Cohort 2 (>6 years to ≤ 12 years) received ETV oral solution, 0.015 mg/kg up to 0.5 mg, once a day (QD) and Cohort 3 (age >12 years to ≤ 18 years) received ETV oral solution,

0.015 mg/kg up to 0.5 mg, or ETV tablets, 0.5 mg, QD. Following PK analysis, those who met the specified dosing requirements (at least 0.5 mg/day) and could tolerate swallowing ETV tablets were allowed to choose either formulation. Entecavir (ETV) was administered for a maximum of 120 weeks.

Reporting group title	Lamivudine (LVD)-experienced (Group B)
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Reporting group description:

Participants with greater than (>) 12 weeks of prior LVD therapy were included in Group B. Prior to PK assessment, Cohort 1 (age ≥ 2 years to ≤ 6 years) and Cohort 2 (> 6 years to ≤ 12 years) received ETV oral solution, 0.030 mg/kg up to 1.0 mg, QD and Cohort 3 (age >12 years to ≤ 18 years) received ETV oral solution, 0.030 mg/kg up to 1.0 mg, or ETV tablets, 1.0 mg QD. Following PK analysis, those who met the specified dosing requirements (at least 1.0 mg/day) and could tolerate swallowing ETV tablets were allowed to choose either formulation. Entecavir (ETV) was administered for a maximum of 120 weeks.

Reporting group title	Nucleoside/tide analog (NA) - experienced (Group C)
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Reporting group description:

Participants who failed previous treatment with any non-ETV nucleoside/tide analog (NA) were included in Group C, starting in 2011. PK assessment was optional to participants in Group C. All participants received ETV oral solution, 0.030 mg/kg up to 1.0 mg, or ETV tablets, 1.0 mg, QD. Participants who met the specified dosing requirements (at least 1.0 mg/day for NA-experienced participants) and could tolerate swallowing ETV tablets were allowed to choose either formulation. ETV was administered for a maximum of 120 weeks.

Primary: Number of Subjects with Serious Adverse Events (SAE) and Discontinuations Due to Adverse Events (AEs) - On Treatment

End point title	Number of Subjects with Serious Adverse Events (SAE) and Discontinuations Due to Adverse Events (AEs) - On Treatment ^[1]
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End point description:

AE=any new unfavorable symptom, sign, or disease or worsening of a preexisting condition that may not have a causal relationship with treatment. SAE=a medical event that at any dose results in death, persistent or significant disability/incapacity, or drug dependency/abuse; is life-threatening, an important medical event, or a congenital anomaly/birth defect; or requires or prolongs hospitalization. Medical Dictionary for Regulatory Activities (MedDRA) version 16.0 was used.

End point type	Primary
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End point timeframe:

Day 1 to Week 120

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 summary statistics were planned for this endpoint.

End point values	Lamivudine (LVD)-naive (Group A)	Lamivudine (LVD)-experienced (Group B)	Nucleoside/tide analog (NA) - experienced (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	19	5	
Units: Subjects				
Serious Adverse Events (n=24, 19, 5)	2	0	0	
Discontinuations Due to AEs (n=24,19,5)	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Maximum Observed Plasma Concentration (Cmax) and Mean Trough Observed Plasma Concentration (Cmin) of Entecavir in LVD-naïve and LVD-experienced Subjects, by Age Cohort

End point title	Mean Maximum Observed Plasma Concentration (Cmax) and Mean Trough Observed Plasma Concentration (Cmin) of Entecavir in LVD-naïve and LVD-experienced Subjects, by Age Cohort
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End point description:

Cmax and Cmin were derived from plasma concentration of ETV versus time and measured in nanograms per milliliters (ng/mL). Blood samples were obtained before study drug administration and at 0.5, 1, 2, 4, 8, and 24 hours after study drug administration on Day 14 (+/- 4 days) for the PK assessment. Plasma samples were analyzed for ETV with a validated method using liquid chromatography-tandem mass spectrometry detection. Note: PK parameters were summarized for only Groups A and B. PK assessment was optional for Group C subjects (NA-experienced subjects who were included with the September 2011 country-specific protocol amendment). No Group C subjects chose to participate in the PK assessment.

End point type	Secondary
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End point timeframe:

Day 14

End point values	Lamivudine (LVD)-naïve (Group A)	Lamivudine (LVD)-experienced (Group B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	19		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Cmax of ETV (≥ 2 yrs to ≤ 6 yrs), (n=7, 3)	8.07 (± 24)	16.03 (± 8)		
Cmax of ETV (> 6 yrs to ≤ 12 yrs), (n=9, 7)	6.29 (± 25)	19.01 (± 15)		
Cmax of ETV (> 12 yrs to ≤ 18 yrs), (n=8,9)	5.11 (± 27)	11.32 (± 37)		
Cmin of ETV (≥ 2 yrs to ≤ 6 yrs), (n=7, 3)	0.244 (± 32)	0.468 (± 17)		
Cmin of ETV (> 6 yrs to ≤ 12 yrs), (n=9, 7)	0.320 (± 22)	0.497 (± 32)		
Cmin of ETV (> 12 yrs to ≤ 18 yrs), (n=8,9)	0.271 (± 25)	0.455 (± 25)		

Statistical analyses

No statistical analyses for this end point

Secondary: Median Time of Maximum Observed Plasma Concentration (Tmax) in LVD-naïve and LVD-experienced Subjects, by Age Cohort

End point title	Median Time of Maximum Observed Plasma Concentration (Tmax) in LVD-naïve and LVD-experienced Subjects, by Age Cohort
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End point description:

Tmax was derived from plasma concentration of ETV versus time and measured in hours (h). Blood

samples were obtained before study drug administration and at 0.5, 1, 2, 4, 8, and 24 hours after study drug administration on Day 14 (+/- 4 days) for the PK assessment. Plasma samples were analyzed for ETV with a validated method using liquid chromatography-tandem mass spectrometry detection. Age categories presented below: subjects age as of first day of dosing. PK assessment was optional for Group C subjects (NA-experienced subjects who were included with the September 2011 country-specific protocol amendment). No Group C subjects chose to participate in the PK assessment.

End point type	Secondary
End point timeframe:	
Day 14	

End point values	Lamivudine (LVD)-naive (Group A)	Lamivudine (LVD)-experienced (Group B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	19		
Units: hr				
median (full range (min-max))				
Tmax of ETV (≥ 2 yrs to ≤ 6 yrs), (n=7, 3)	0.50 (0.5 to 1.0)	1.00 (0.5 to 1.5)		
Tmax of ETV (> 6 yrs to ≤ 12 yrs), (n=9, 7)	0.57 (0.5 to 2.0)	0.72 (0.5 to 1.0)		
Tmax of ETV (> 12 yrs to ≤ 18 yrs), (n=8,9)	0.78 (0.5 to 1.0)	0.52 (0.5 to 1.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Area Under the Concentration-Time Curve in One Dosing Interval [AUC(TAU)] of Entecavir in LVD-naive and LVD-experienced Subjects, by Age Cohort

End point title	Mean Area Under the Concentration-Time Curve in One Dosing Interval [AUC(TAU)] of Entecavir in LVD-naive and LVD-experienced Subjects, by Age Cohort
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End point description:

Area under the Curve (AUC) was derived from plasma concentration of ETV versus time. AUC(TAU) was calculated by log- and linear trapezoidal summations, TAU = 24 hours, and was measured in nanograms*hours per milliliter (ng*h/mL). Blood samples were obtained before study drug administration and at 0.5, 1, 2, 4, 8, and 24 hours after study drug administration on Day 14 (+/- 4 days) for the PK assessment. Plasma samples were analyzed for ETV with a validated method using liquid chromatography-tandem mass spectrometry detection. PK assessment was optional for Group C subjects (NA-experienced subjects who were included with the September 2011 country-specific protocol amendment). No Group C subjects chose to participate in the PK assessment.

End point type	Secondary
End point timeframe:	
Day 14	

End point values	Lamivudine (LVD)-naive (Group A)	Lamivudine (LVD)-experienced (Group B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	19		
Units: ng*h/mL				
geometric mean (geometric coefficient of variation)				
AUC(TAU) of ETV (≥ 2 yrs to ≤ 6 yrs), (n=7, 3)	18.69 (± 21)	42.26 (± 27)		
AUC(TAU) of ETV (> 6 yrs to ≤ 12 yrs), (n=9, 7)	20.42 (± 20)	41.50 (± 21)		
AUC(TAU) of ETV (> 12 yrs to ≤ 18 yrs), (n=8,9)	15.96 (± 22)	35.36 (± 24)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Apparent Total Body Clearance (CLT/F) of Entecavir in LVD-naive and LVD-experienced Subjects, by Age Cohort

End point title	Mean Apparent Total Body Clearance (CLT/F) of Entecavir in LVD-naive and LVD-experienced Subjects, by Age Cohort
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End point description:

CLT/F was calculated by dividing the dose of ETV by AUC(TAU) of ETV and was measured in liters per hour (L/h). Blood samples were obtained before study drug administration and at 0.5, 1, 2, 4, 8, and 24 hours after study drug administration on Day 14 (+/- 4 days) for the PK assessment. Plasma samples were analyzed for ETV with a validated method using liquid chromatography-tandem mass spectrometry detection. PK assessment was optional for Group C subjects (NA-experienced subjects who were included with the September 2011 country-specific protocol amendment). No Group C subjects chose to participate in the PK assessment.

End point type	Secondary
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End point timeframe:

At 2 weeks

End point values	Lamivudine (LVD)-naive (Group A)	Lamivudine (LVD)-experienced (Group B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	19		
Units: L/h				
arithmetic mean (standard deviation)				
CLT/F of ETV (≥ 2 yrs to ≤ 6 yrs), (n=7, 3)	11.40 (± 2.564)	12.31 (± 3.102)		
CLT/F of ETV (> 6 yrs to ≤ 12 yrs), (n=9, 7)	22.66 (± 6.134)	21.67 (± 6.940)		
CLT/F of ETV (> 12 yrs to ≤ 18 yrs), (n=8,9)	31.92 (± 6.429)	28.95 (± 6.496)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with HBV DNA Less than 50 IU/mL through Week 96 in Treated Subjects

End point title	Number of Subjects with HBV DNA Less than 50 IU/mL through Week 96 in Treated Subjects
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End point description:

Hepatitis B virus DNA by polymerase chain reaction (PCR) was measured using the Roche COBAS TaqMan - high pure system (HPS) assay and was reported in international units per milliliter (IU/mL). Baseline was the last value measured prior to or on the date of the first dose of study therapy. The intent-to-treat method of Non-Completer = Failure was used through Week 48 in which all treated subjects were analyzed, and participants with missing data at the analysis week were considered failures. After Week 48, the method of Non-Completer = Missing was used, in which subjects with missing data at the analysis week were excluded.

End point type	Secondary
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End point timeframe:

Baseline to Week 96

End point values	Lamivudine (LVD)-naive (Group A)	Lamivudine (LVD)-experienced (Group B)	Nucleoside/tide analog (NA) - experienced (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	19	5	
Units: Subjects				
Baseline (n=24,19,5)	0	0	0	
Week 12 (n=24,19,5)	1	0	0	
Week 24 (n=24,19,5)	10	3	0	
Week 36 (n=24,19,5)	11	6	0	
Week 48 (n=24,19,5)	14	9	0	
Week 96 (n=12,13,4)	8	11	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Hepatitis B e antigen (HBeAg) Loss through Week 96 in Treated Subjects

End point title	Number of Subjects with Hepatitis B e antigen (HBeAg) Loss through Week 96 in Treated Subjects
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End point description:

HBeAg loss: HBeAg negative. The method used for the detection of HBe Ag was the DiaSorin - Anti HBe enzyme immunoassay kit. Baseline was the last value measured prior to or on the date of the first dose of study therapy. The intent-to-treat method of Non-Completer = Failure was used through Week 48 in which all treated subjects were analyzed, and participants with missing data at the analysis week were considered failures. After Week 48, the method of Non-Completer = Missing was used, in which subjects with missing data at the analysis week were excluded.

End point type	Secondary
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End point timeframe:

Baseline to Week 96

End point values	Lamivudine (LVD)-naive (Group A)	Lamivudine (LVD)-experienced (Group B)	Nucleoside/tide analog (NA) - experienced (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	19	5	
Units: Subjects				
Baseline (n=24,19,5)	0	0	0	
Week 12 (n=24,19,5)	3	0	0	
Week 24 (n=24,19,5)	4	1	0	
Week 36 (n=23,19,5)	5	1	0	
Week 48 (n=24,19,5)	10	3	0	
Week 96 (n=12,13,4)	5	2	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Hepatitis B s antigen (HBsAg) Loss through Week 96 in Treated Subjects

End point title	Number of Subjects with Hepatitis B s antigen (HBsAg) Loss through Week 96 in Treated Subjects
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End point description:

HBsAg loss: HBsAg negative. The method used for detection of HBsAg was the ADVIA Centaur iImmunoassay system. Baseline was the last value measured prior to or on the date of the first dose of study therapy. The intent-to-treat method of Non-Completer = Failure was used through Week 48 in which all treated subjects were analyzed, and participants with missing data at the analysis week were considered failures. After Week 48, the method of Non-Completer = Missing was used, in which subjects with missing data at the analysis week were excluded.

End point type	Secondary
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End point timeframe:

Baseline to Week 96

End point values	Lamivudine (LVD)-naive (Group A)	Lamivudine (LVD)-experienced (Group B)	Nucleoside/tide analog (NA) - experienced (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	19	5	
Units: Subjects				
Baseline (n=24,19,5)	0	0	0	
Week 12 (n=24,19,5)	0	0	0	
Week 24 (n=24,19,5)	0	0	0	
Week 36 (n=24,19,5)	1	0	0	
Week 48 (n=24,19,5)	1	0	0	
Week 96 (n=12,13,4)	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Hepatitis B e antigen Seroconversion through Week 96 in Treated Subjects

End point title	Number of Subjects with Hepatitis B e antigen Seroconversion through Week 96 in Treated Subjects
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End point description:

HBe seroconversion: loss of HBeAg (HBeAg negative) with positive HB e antibodies (HBeAb), ie both the presence of HBeAb and the absence of HBeAg. The method used for the detection HBeAg seroconversion was the DiaSorin - Anti HBe enzyme immunoassay kit. Baseline was the last value measured prior to or on the date of the first dose of study therapy. The intent-to-treat method of Non-Completer = Failure was used through Week 48 in which all treated subjects were analyzed, and participants with missing data at the analysis week were considered failures. After Week 48, the method of Non-Completer = Missing was used, in which subjects with missing data at the analysis week were excluded.

End point type	Secondary
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End point timeframe:

Baseline through Week 96

End point values	Lamivudine (LVD)-naive (Group A)	Lamivudine (LVD)-experienced (Group B)	Nucleoside/tide analog (NA) - experienced (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	19	5	
Units: Subjects				
Baseline (n=24,19,5)	0	0	0	
Week 12 (n=24,19,5)	3	0	0	
Week 24 (n=24,19,5)	4	1	0	
Week 36 (n=24,19,5)	5	1	0	
Week 48 (n=24,19,5)	10	3	0	
Week 96 (n=12,13,4)	5	1	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with HBV DNA Less than Lower Limit of Detection (LLD) for the Roche COBAS TaqMan - HPS assay at Week 96 in Treated Subjects

End point title	Number of Subjects with HBV DNA Less than Lower Limit of Detection (LLD) for the Roche COBAS TaqMan - HPS assay at Week 96 in Treated Subjects
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End point description:

Hepatitis B virus DNA by PCR was measured using the Roche COBAS TaqMan - HPS assay and was reported in IU/mL. LLD = 6 IU/mL. Baseline was the last value measured prior to or on the date of the first dose of study therapy. The intent-to-treat method of Non-Completer = Failure was used through Week 48 in which all treated subjects were analyzed, and participants with missing data at the analysis week were considered failures. After Week 48, the method of Non-Completer = Missing was used, in which subjects with missing data at the analysis week were excluded.

End point type	Secondary
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End point timeframe:

Baseline to Week 96

End point values	Lamivudine (LVD)-naive (Group A)	Lamivudine (LVD)-experienced (Group B)	Nucleoside/tide analog (NA) - experienced (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	19	5	
Units: Subjects				
Baseline (n=24,19,5)	0	0	0	
Week 12 (n=24,19,5)	1	0	0	
Week 24 (n=24,19,5)	6	1	0	
Week 36 (n=24,19,5)	7	5	0	
Week 48 (n=24,19,5)	13	6	0	
Week 96 (n=12,13,4)	8	8	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With HBV DNA Less Than Lower Limit of Quantification (LLQ) for the Roche COBAS TaqMan - HPS Assay through Week 96 in Treated Subjects

End point title	Number of Subjects With HBV DNA Less Than Lower Limit of Quantification (LLQ) for the Roche COBAS TaqMan - HPS Assay through Week 96 in Treated Subjects
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End point description:

Hepatitis B virus DNA by PCR was measured using the Roche COBAS TaqMan - HPS assay and was reported in IU/mL. LLQ = 29 IU/mL. Baseline was the last value measured prior to or on the date of the first dose of study therapy. The intent-to-treat method of Non-Completer = Failure was used through Week 48 in which all treated subjects were analyzed, and participants with missing data at the analysis week were considered failures. After Week 48, the method of Non-Completer = Missing was used, in which subjects with missing data at the analysis week were excluded.

End point type	Secondary
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End point timeframe:
Baseline through Week 96

End point values	Lamivudine (LVD)-naive (Group A)	Lamivudine (LVD)-experienced (Group B)	Nucleoside/tide analog (NA) - experienced (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	19	5	
Units: Subjects				
Baseline (n=24,19,5)	0	0	0	
Week 12 (n=24,19,5)	1	0	0	
Week 24 (n=24,19,5)	9	2	0	
Week 36 (n=24,19,5)	10	5	0	
Week 48 (n=24,19,5)	14	7	0	
Week 96 (n=12,13,4)	8	8	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with HB s Antigen (HBsAg) Seroconversion through Week 96 in Treated Subjects

End point title	Number of Subjects with HB s Antigen (HBsAg) Seroconversion through Week 96 in Treated Subjects
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End point description:

HB s Ag seroconversion: loss of HBsAg (HBsAg negative) and presence of HB s antibodies (HBsAb). The method used for the detection of HBsAg seroconversion was the ADVIA Centaur iImmunoassay system. Baseline was the last value measured prior to or on the date of the first dose of study therapy. The intent-to-treat method of Non-Completer = Failure was used through Week 48 in which all treated subjects were analyzed, and participants with missing data at the analysis week were considered failures. After Week 48, the method of Non-Completer = Missing was used, in which subjects with missing data at the analysis week were excluded.

End point type	Secondary
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End point timeframe:

Baseline through Week 96

End point values	Lamivudine (LVD)-naive (Group A)	Lamivudine (LVD)-experienced (Group B)	Nucleoside/tide analog (NA) - experienced (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	19	5	
Units: Subjects				
Baseline (n=24,19,5)	0	0	0	
Week 12 (n=24,19,5)	0	0	0	
Week 24 (n=24,19,5)	0	0	0	

Week 36 (n=24,19,5)	0	0	0	
Week 48 (n=24,19,5)	0	0	0	
Week 96 (n=12,13,4)	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects who had a Protocol Defined Response (PDR) through Week 96 in Treated Subjects

End point title	Number of Subjects who had a Protocol Defined Response (PDR) through Week 96 in Treated Subjects
End point description: PDR was defined as confirmed HBV DNA < 50 IU/mL plus confirmed HBeAg seroconversion on 2 sequential measurements at least 14 days apart. Baseline was the last value measured prior to or on the date of the first dose of study therapy. The intent-to-treat method of Non-Completer = Failure was used through Week 48 in which all treated subjects were analyzed, and participants with missing data at the analysis week were considered failures. After Week 48, the method of Non-Completer = Missing was used, in which subjects with missing data at the analysis week were excluded.	
End point type	Secondary
End point timeframe: Baseline to Week 96	

End point values	Lamivudine (LVD)-naive (Group A)	Lamivudine (LVD)-experienced (Group B)	Nucleoside/tide analog (NA) - experienced (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	19	5	
Units: Subjects				
Week 12 (n=24,19,5)	0	0	0	
Week 24 (n=24,19,5)	4	0	0	
Week 36 (n=24,19,5)	4	1	0	
Week 48 (n=24,19,5)	7	3	0	
Week 96 (n=12,13,4)	3	1	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Log10 Change from Baseline in HBV DNA using Roche COBAS TaqMan - HPS through Week 96 in Treated Subjects

End point title	Mean Log10 Change from Baseline in HBV DNA using Roche COBAS TaqMan - HPS through Week 96 in Treated Subjects
End point description: Hepatitis B virus DNA by PCR was measured using the Roche COBAS TaqMan - HPS assay and was reported in IU/mL. HBV DNA log10 changes from baseline were summarized over time.	

End point type	Secondary
End point timeframe:	
Baseline to Week 96	

End point values	Lamivudine (LVD)-naive (Group A)	Lamivudine (LVD)-experienced (Group B)	Nucleoside/tide analog (NA) - experienced (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	19	5	
Units: IU/mL				
arithmetic mean (standard error)				
Week 12 (n=22,17,5)	-4.45 (± 0.2418)	-3.89 (± 0.1592)	-3.80 (± 0.4657)	
Week 24 (n=24,18,5)	-5.30 (± 0.2744)	-4.85 (± 0.2900)	-3.89 (± 0.5440)	
Week 36 (n=21,19,5)	-5.61 (± 0.2580)	-5.14 (± 0.2604)	-3.90 (± 0.2499)	
Week 48 (n=22,18,5)	-5.86 (± 0.2176)	-5.36 (± 0.3032)	-4.32 (± 0.4794)	
Week 96 (n=12,13,4)	-6.30 (± 0.2576)	-5.86 (± 0.2222)	-5.79 (± 0.5308)	

Statistical analyses

No statistical analyses for this end point

Secondary: Alanine aminotransferase (ALT) Normalization from Baseline through Week 96 in Treated Subjects

End point title	Alanine aminotransferase (ALT) Normalization from Baseline through Week 96 in Treated Subjects
End point description:	
Normalization in ALT= $ALT \leq 1.0 \times \text{upper limit of normal (ULN)}$. Baseline was the last value measured prior to or on the date of the first dose of study therapy. The intent-to-treat method of Non-Completer = Failure was used through Week 48 in which all treated subjects were analyzed, and participants with missing data at the analysis week were considered failures. After Week 48, the method of Non-Completer = Missing was used, in which subjects with missing data at the analysis week were excluded.	
End point type	Secondary
End point timeframe:	
Baseline to Week 96	

End point values	Lamivudine (LVD)-naive (Group A)	Lamivudine (LVD)-experienced (Group B)	Nucleoside/tide analog (NA) - experienced (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	19	5	
Units: Subjects				
Baseline (n=24,19,5)	0	1	2	

Week 4 (n=24,19,5)	1	1	2	
Week 8 (n=24,19,5)	3	2	2	
Week 12 (n=24,19,5)	5	7	3	
Week 18 (n=24,19,5)	15	10	5	
Week 24 (n=24,19,5)	15	12	5	
Week 30 (n=24,19,5)	16	13	5	
Week 36 (n=24,19,5)	16	16	5	
Week 42 (n=24,19,5)	16	15	5	
Week 48 (n=24,19,5)	20	18	4	
Week 96 (n=11,13,4)	10	13	3	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with HBV DNA by PCR Categories at Weeks 48 and 96 in Treated Subjects

End point title	Number of Subjects with HBV DNA by PCR Categories at Weeks 48 and 96 in Treated Subjects
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End point description:

Hepatitis B virus DNA by PCR was measured using the Roche COBAS TaqMan - HPS assay and was reported in IU/mL. LLQ = 29 IU/mL. Baseline was the last value measured prior to or on the date of the first dose of study therapy. The intent-to-treat method of Non-Completer = Failure was used through Week 48 in which all treated subjects were analyzed, and participants with missing data at the analysis week were considered failures. After Week 48, the method of Non-Completer = Missing was used, in which subjects with missing data at the analysis week were excluded.

End point type	Secondary
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End point timeframe:

Baseline, Week 48, Week 96

End point values	Lamivudine (LVD)-naïve (Group A)	Lamivudine (LVD)-experienced (Group B)	Nucleoside/tide analog (NA) - experienced (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	19	5	
Units: Subjects				
Baseline $\geq 17,200$ IU/mL (n=24,19,5)	24	19	5	
Week 48: < 50 IU/mL (n=22,19,5)	14	9	0	
Week 48: $50 - < 172$ IU/mL (n=22,19,5)	1	2	0	
Week 48: $172 - < 1720$ IU/mL (n=22,19,5)	3	3	1	
Week 48: $1720 - < 17,200$ IU/mL (n=22,19,5)	3	1	3	
Week 48: $\geq 17,200$ IU/mL (n=22,19,5)	1	3	1	
Week 96: < 50 IU/mL (n=12,13,4)	8	11	2	
Week 96: $50 - < 172$ IU/mL (n=12,13,4)	1	1	0	

Week 96: 172 - < 1720 IU/mL (n=12,13,4)	3	0	1	
Week 96: 1720 - < 17,200 IU/mL (n=12,13,4)	0	1	1	
Week 96: > = 17,200 IU/mL (n=12,13,4)	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with a Combination of ALT Normalization and HBV DNA Less than 50 IU/mL Through Week 96 in Treated Subjects

End point title	Number of Subjects with a Combination of ALT Normalization and HBV DNA Less than 50 IU/mL Through Week 96 in Treated Subjects
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End point description:

Hepatitis B virus DNA by PCR was measured using the Roche COBAS TaqMan - HPS assay and was reported in IU/mL. Baseline was the last value measured prior to or on the date of the first dose of study therapy. Normalization in ALT= ALT ≤ 1.0*ULN. The intent-to-treat method of Non-Completer = Failure was used through Week 48 in which all treated subjects were analyzed, and participants with missing data at the analysis week were considered failures. After Week 48, the method of Non-Completer = Missing was used, in which subjects with missing data at the analysis week were excluded.

End point type	Secondary
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End point timeframe:

Baseline to Week 96

End point values	Lamivudine (LVD)-naive (Group A)	Lamivudine (LVD)-experienced (Group B)	Nucleoside/tide analog (NA) - experienced (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	19	5	
Units: Subjects				
Baseline (n=24,19,5)	0	0	0	
Week 12 (n=24, 19, 5)	0	0	0	
Week 24 (n=24, 19, 5)	10	3	0	
Week 36 (n=24, 19, 5)	11	4	0	
Week 48 (n=24, 19, 5)	13	9	0	
Week 96 (n=12,13,4)	7	11	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with a Combination of ALT Normalization and HBV DNA Less than 50 IU/mL, plus HBeAg Seroconversion Through Week 96 in Treated Subjects

End point title	Number of Subjects with a Combination of ALT Normalization and HBV DNA Less than 50 IU/mL, plus HBeAg Seroconversion Through Week 96 in Treated Subjects
End point description:	
Hepatitis B virus DNA by PCR was measured using the Roche COBAS TaqMan - HPS assay and was reported in IU/mL. Baseline was the last value measured prior to or on the date of the first dose of study therapy. Normalization in ALT= ALT \leq 1.0*ULN. HBe seroconversion was determination of presence of HBeAb and loss of HBeAg. The method used for the detection of HBeAg seroconversion was the DiaSorin - Anti HBe enzyme immunoassay kit. The intent-to-treat method of Non-Completer = Failure was used through Week 48 in which all treated subjects were analyzed, and participants with missing data at the analysis week were considered failures. After Week 48, the method of Non-Completer = Missing was used, in which subjects with missing data at the analysis week were excluded.	
End point type	Secondary
End point timeframe:	
Baseline to Week 96	

End point values	Lamivudine (LVD)-naive (Group A)	Lamivudine (LVD)-experienced (Group B)	Nucleoside/tide analog (NA) - experienced (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	19	5	
Units: Subjects				
Baseline (n=24,19,5)	0	0	0	
Week 12 (n=24,19,5)	0	0	0	
Week 24 (n=24,19,5)	4	0	0	
Week 36 (n=24,19,5)	4	1	0	
Week 48 (n=24,19,5)	8	3	0	
Week 96 (n=11,13,4)	3	1	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with a Combination of ALT Normalization and HBV DNA Less than 50 IU/mL, without HBeAg Seroconversion, Through Week 96 in Treated Subjects

End point title	Number of Subjects with a Combination of ALT Normalization and HBV DNA Less than 50 IU/mL, without HBeAg Seroconversion, Through Week 96 in Treated Subjects
End point description:	
Hepatitis B virus DNA by PCR was measured using the Roche COBAS TaqMan - HPS assay and was reported in IU/mL. Baseline was the last value measured prior to or on the date of the first dose of study therapy. Normalization in ALT= ALT \leq 1.0*ULN. HBe seroconversion: loss of HBeAg (HBeAg negative) with positive HBeAb. The method used for the detection of HBeAg/Ab serologies was the DiaSorin enzyme immunoassay kit. The intent-to-treat method of Non-Completer = Failure was used through Week 48 in which all treated subjects were analyzed, and participants with missing data at the analysis week were considered failures. After Week 48, the method of Non-Completer = Missing was used, in which subjects with missing data at the analysis week were excluded.	
End point type	Secondary
End point timeframe:	
Baseline to Week 96	

End point values	Lamivudine (LVD)-naive (Group A)	Lamivudine (LVD)-experienced (Group B)	Nucleoside/tide analog (NA) - experienced (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	19	5	
Units: Subjects				
Baseline (n=24,19,5)	0	0	0	
Week 12 (n=24,19,5)	0	0	0	
Week 24 (n=24,19,5)	6	3	0	
Week 36 (n=24,19,5)	7	3	0	
Week 48 (n=24,19,5)	5	6	0	
Week 96 (n=12,13,4)	4	10	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Hematology Laboratory Abnormalities (Grades 1 - 4) - On Treatment - Treated Subjects

End point title	Number of Subjects with Hematology Laboratory Abnormalities (Grades 1 - 4) - On Treatment - Treated Subjects
End point description:	
Toxicity Scale: Division of AIDs (DAIDS) grades Version 1.0. Upper limit of normal (ULN); lower limit of normal (LLN); Cells per Liter (c/L); cells per microliter (c/μL); grams per deciliter (g/dL); milliequivalents per liter (mEq/L); cells per microliter (c/μL): Grade (Gr). Hemoglobin g/dL: Gr1:10.0-10.9;Gr2: 9.0-9.9; Gr3:7.0-8.9; Gr4: <7.0. International normalization ratio (INR): Gr1:1.1-<1.5*ULN; Gr2: 1.6-<2.0*ULN; Gr3: 2.1-3.0*ULN;Gr4: >3.0*ULN. Neutrophils/bands c/μL: Gr1;1.0-1.3*10 ³ ; Gr2: 0.75-0.99*10 ³ ; Gr 3: 0.50-0.749*10 ³ ; Gr4: <0.5*10 ³ .	
End point type	Secondary
End point timeframe:	
Day 1 to Week 120	

End point values	Lamivudine (LVD)-naive (Group A)	Lamivudine (LVD)-experienced (Group B)	Nucleoside/tide analog (NA) - experienced (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	19	5	
Units: Subjects				
Hemoglobin	1	0	1	
International normalization ratio	4	3	0	
Neutrophils (absolute) + bands	3	3	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Chemistry Laboratory Abnormalities (Grades 1 - 4) - On Treatment - Treated Subjects

End point title	Number of Subjects with Chemistry Laboratory Abnormalities (Grades 1 - 4) - On Treatment - Treated Subjects
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End point description:

Toxicity Scale: DAIDS Version 1.0 and modified World Health Organization (WHO). Grade (Gr). ALT: Gr1:1.25-<2.5*ULN; Gr2: 2.6-<5.0 *ULN; Gr3: 5.1-10.0*ULN; Gr4:>10.0*ULN. Aspartate aminotransferase (AST): Gr1: 1.25-<2.5*ULN; Gr2:2.6-<5.0*ULN; Gr 3: 5.1-10.0*ULN; Gr4>10.0*ULN. Alkaline phosphatase: Gr1:1.25-<2.5*ULN; Gr2: 2.6-<5.0*ULN; Gr3: 5.1-10.0*ULN; Gr4: >10.0*ULN. Lipase: Gr1:1.1-<1.5*ULN;Gr2:1.6-<3.0*ULN; Gr3: 3.1-5.0*ULN; Gr4: >5.0*ULN. Creatinine: Gr1: 1.1-1.3*ULN; Gr2: 1.4-<1.8*ULN; Gr3: 1.9 - <3.4*ULN; Gr4: >=3.5*ULN. Glucose mg/dL (high): Gr1:110-<125 (Fasting)/116-<160;Gr2:126-<250 (F)/161-<250; Gr3: 251-500; Gr4: >500.Glucose (low): Gr1: 55-64; Gr2: 40 - <54; Gr3: 30-39; Gr4: <30 mg/dL.

End point type	Secondary
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End point timeframe:

Day 1 to Week 120

End point values	Lamivudine (LVD)-naive (Group A)	Lamivudine (LVD)-experienced (Group B)	Nucleoside/tide analog (NA) - experienced (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	19	5	
Units: Subjects				
ALT	23	17	4	
AST	14	9	1	
Alkaline Phosphatase	3	3	0	
Lipase	5	12	3	
Creatinine	1	1	0	
Glucose, high	3	4	1	
Glucose, low	3	4	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Electrolyte Laboratory Abnormalities (Grades 1 - 4) - On Treatment - Treated Subjects

End point title	Number of Subjects with Electrolyte Laboratory Abnormalities (Grades 1 - 4) - On Treatment - Treated Subjects
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End point description:

Toxicity Scale: DAIDS Version 1.0 and modified World Health Organization (WHO) for chloride. Milliequivalents per liter (mEq/L); Grade (Gr). Chloride high (mEq/L): Gr1: 113-<117; Gr2: 117-<121; Gr3: 121-125; Gr4: >125. Potassium low (mEq/L): Gr1: 3.0-3.4; Gr2: 2.5-2.9; Gr3:2.0-<2.4; Gr4: <2.0. Potassium high: Gr1; 5.6- <6.0; Gr2: 6.1-<6.5; Gr3: 6.6-7.0; Gr4: >7.0. Sodium high (mEq/L): Gr1; 146-<150; Gr2: 151-<154; Gr3: 155-<159; Gr4: >=160.

End point type	Secondary
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End point timeframe:

Day 1 Week 120

End point values	Lamivudine (LVD)-naive (Group A)	Lamivudine (LVD)- experienced (Group B)	Nucleoside/tide analog (NA) - experienced (Group C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	19	5	
Units: Subjects				
Chloride, high	3	0	0	
Potassium, low	1	0	0	
Potassium, high	1	1	0	
Sodium, high	4	3	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From study initiation to study completion (June 2007 to September 2017, approximately 118 months)

Adverse event reporting additional description:

From first dose to date of last dose plus 5 days

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.0
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Reporting groups

Reporting group title	LVD-naive
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Reporting group description:

Subjects who have not received LVD therapy within 24 weeks were treated with age stratified oral dose of Entecavir (ETV) 0.015 milligram (mg) per kilogram (kg) up to a maximum dose of 0.5 mg once daily (QD). Subjects with age ranging 2-6 years received treatment as solution, while subjects ranging from 6-12 and 12-18 years received treatment as either solution or tablet based on subject's convenience for up to maximum of 120 weeks.

Reporting group title	NA-experienced
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Reporting group description:

Subjects who had failed previous treatment with any non-ETV NA therapy were treated with age stratified oral dose of ETV 0.030 mg/kg up to a maximum of 1.0 mg QD. Subjects with age ranging 2-6 years received treatment as solution, while subjects ranging from 6-12 and 12-18 years received treatment as either solution or tablet based on subject's convenience for up to maximum of 120 weeks.

Reporting group title	LVD-experienced
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Reporting group description:

Subjects who have received LVD therapy before 12 weeks were treated with age stratified oral dose of ETV 0.030 mg/kg up to a maximum of 1.0 mg QD. Subjects with age ranging 2-6 years received treatment as solution, while subjects ranging from 6-12 and 12-18 years received treatment as either solution or tablet based on subject's convenience for up to maximum of 120 weeks.

Serious adverse events	LVD-naive	NA-experienced	LVD-experienced
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 24 (8.33%)	0 / 5 (0.00%)	0 / 19 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 24 (4.17%)	0 / 5 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			

subjects affected / exposed	1 / 24 (4.17%)	0 / 5 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 24 (4.17%)	0 / 5 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lobar pneumonia			
subjects affected / exposed	1 / 24 (4.17%)	0 / 5 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	LVD-naïve	NA-experienced	LVD-experienced
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 24 (87.50%)	4 / 5 (80.00%)	17 / 19 (89.47%)
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 24 (0.00%)	1 / 5 (20.00%)	0 / 19 (0.00%)
occurrences (all)	0	3	0
Fatigue			
subjects affected / exposed	1 / 24 (4.17%)	0 / 5 (0.00%)	2 / 19 (10.53%)
occurrences (all)	1	0	2
Influenza like illness			
subjects affected / exposed	1 / 24 (4.17%)	0 / 5 (0.00%)	2 / 19 (10.53%)
occurrences (all)	2	0	2
Pyrexia			
subjects affected / exposed	10 / 24 (41.67%)	1 / 5 (20.00%)	5 / 19 (26.32%)
occurrences (all)	16	1	6
Product taste abnormal			
subjects affected / exposed	1 / 24 (4.17%)	0 / 5 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Immune system disorders			

Seasonal allergy subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	0 / 5 (0.00%) 0	1 / 19 (5.26%) 1
Respiratory, thoracic and mediastinal disorders			
Bronchospasm subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 3	0 / 5 (0.00%) 0	0 / 19 (0.00%) 0
Cough subjects affected / exposed occurrences (all)	7 / 24 (29.17%) 8	1 / 5 (20.00%) 2	5 / 19 (26.32%) 5
Epistaxis subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2	0 / 5 (0.00%) 0	1 / 19 (5.26%) 1
Nasal congestion subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 3	0 / 5 (0.00%) 0	1 / 19 (5.26%) 2
Oropharyngeal pain subjects affected / exposed occurrences (all)	3 / 24 (12.50%) 3	0 / 5 (0.00%) 0	1 / 19 (5.26%) 1
Rhinorrhoea subjects affected / exposed occurrences (all)	3 / 24 (12.50%) 3	1 / 5 (20.00%) 2	1 / 19 (5.26%) 2
Psychiatric disorders			
Anxiety subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	0 / 5 (0.00%) 0	1 / 19 (5.26%) 1
Mood swings subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	0 / 5 (0.00%) 0	1 / 19 (5.26%) 1
Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2	0 / 5 (0.00%) 0	0 / 19 (0.00%) 0
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	0 / 5 (0.00%) 0	2 / 19 (10.53%) 2

Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 24 (0.00%)	0 / 5 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Joint injury			
subjects affected / exposed	0 / 24 (0.00%)	0 / 5 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Ligament sprain			
subjects affected / exposed	2 / 24 (8.33%)	0 / 5 (0.00%)	0 / 19 (0.00%)
occurrences (all)	3	0	0
Limb injury			
subjects affected / exposed	2 / 24 (8.33%)	1 / 5 (20.00%)	0 / 19 (0.00%)
occurrences (all)	2	1	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 24 (8.33%)	0 / 5 (0.00%)	0 / 19 (0.00%)
occurrences (all)	2	0	0
Headache			
subjects affected / exposed	7 / 24 (29.17%)	0 / 5 (0.00%)	5 / 19 (26.32%)
occurrences (all)	9	0	9
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 24 (0.00%)	0 / 5 (0.00%)	2 / 19 (10.53%)
occurrences (all)	0	0	2
Tinnitus			
subjects affected / exposed	0 / 24 (0.00%)	1 / 5 (20.00%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Eye haemorrhage			
subjects affected / exposed	0 / 24 (0.00%)	0 / 5 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Ocular hyperaemia			
subjects affected / exposed	0 / 24 (0.00%)	1 / 5 (20.00%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	4 / 24 (16.67%)	1 / 5 (20.00%)	4 / 19 (21.05%)
occurrences (all)	4	1	7
Abdominal pain upper			
subjects affected / exposed	2 / 24 (8.33%)	0 / 5 (0.00%)	1 / 19 (5.26%)
occurrences (all)	2	0	4
Dental caries			
subjects affected / exposed	1 / 24 (4.17%)	0 / 5 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Diarrhoea			
subjects affected / exposed	5 / 24 (20.83%)	1 / 5 (20.00%)	3 / 19 (15.79%)
occurrences (all)	7	1	3
Enteritis			
subjects affected / exposed	1 / 24 (4.17%)	0 / 5 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Soft stool			
subjects affected / exposed	0 / 24 (0.00%)	0 / 5 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Flatulence			
subjects affected / exposed	0 / 24 (0.00%)	0 / 5 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 24 (0.00%)	1 / 5 (20.00%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Mouth ulceration			
subjects affected / exposed	2 / 24 (8.33%)	0 / 5 (0.00%)	0 / 19 (0.00%)
occurrences (all)	3	0	0
Nausea			
subjects affected / exposed	2 / 24 (8.33%)	0 / 5 (0.00%)	0 / 19 (0.00%)
occurrences (all)	3	0	0
Odynophagia			
subjects affected / exposed	0 / 24 (0.00%)	0 / 5 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Tooth impacted			
subjects affected / exposed	0 / 24 (0.00%)	0 / 5 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1

Vomiting subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 4	1 / 5 (20.00%) 2	4 / 19 (21.05%) 4
Skin and subcutaneous tissue disorders			
Acne subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	0 / 5 (0.00%) 0	2 / 19 (10.53%) 2
Dermatitis allergic subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 5 (20.00%) 1	0 / 19 (0.00%) 0
Dermatitis bullous subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 5 (20.00%) 1	0 / 19 (0.00%) 0
Pruritus subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	0 / 5 (0.00%) 0	1 / 19 (5.26%) 1
Rash subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 3	1 / 5 (20.00%) 4	2 / 19 (10.53%) 2
Rash macular subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 5 (20.00%) 1	0 / 19 (0.00%) 0
Rash maculo-papular subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 5 (20.00%) 1	0 / 19 (0.00%) 0
Rash pruritic subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	0 / 5 (0.00%) 0	1 / 19 (5.26%) 1
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 2	1 / 5 (20.00%) 1	0 / 19 (0.00%) 0
Myalgia subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2	0 / 5 (0.00%) 0	1 / 19 (5.26%) 1
Infections and infestations			

Ear infection			
subjects affected / exposed	1 / 24 (4.17%)	0 / 5 (0.00%)	2 / 19 (10.53%)
occurrences (all)	2	0	2
Gastroenteritis			
subjects affected / exposed	1 / 24 (4.17%)	0 / 5 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Gastroenteritis viral			
subjects affected / exposed	0 / 24 (0.00%)	0 / 5 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Impetigo			
subjects affected / exposed	2 / 24 (8.33%)	0 / 5 (0.00%)	0 / 19 (0.00%)
occurrences (all)	2	0	0
Influenza			
subjects affected / exposed	0 / 24 (0.00%)	0 / 5 (0.00%)	2 / 19 (10.53%)
occurrences (all)	0	0	3
Lyme disease			
subjects affected / exposed	0 / 24 (0.00%)	0 / 5 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Molluscum contagiosum			
subjects affected / exposed	0 / 24 (0.00%)	1 / 5 (20.00%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Mumps			
subjects affected / exposed	0 / 24 (0.00%)	0 / 5 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Otitis externa			
subjects affected / exposed	2 / 24 (8.33%)	0 / 5 (0.00%)	0 / 19 (0.00%)
occurrences (all)	2	0	0
Otitis media acute			
subjects affected / exposed	0 / 24 (0.00%)	0 / 5 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Pharyngotonsillitis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 5 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Sinusitis			
subjects affected / exposed	3 / 24 (12.50%)	0 / 5 (0.00%)	0 / 19 (0.00%)
occurrences (all)	3	0	0

Tonsillitis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 5 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	3
Upper respiratory tract infection			
subjects affected / exposed	10 / 24 (41.67%)	2 / 5 (40.00%)	3 / 19 (15.79%)
occurrences (all)	21	2	4
Nasopharyngitis			
subjects affected / exposed	4 / 24 (16.67%)	1 / 5 (20.00%)	9 / 19 (47.37%)
occurrences (all)	12	2	11
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 24 (0.00%)	0 / 5 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 April 2008	Changes incorporated in this amendment are: 1) Incorporate new information regarding the potential anti-HIV effect of entecavir 2) Recent changes in study personnel 3) Adding that the Schwartz method for calculating estimated creatinine clearance should be used in subjects 17 years of age, and the Cockcroft-Gault equation should be used in subjects 18 years of age 4) Clarify labeling and storage of study drug 5) Extending the period of time between the Screening Visit and Day 1 Visit from 4 weeks to 6 weeks in order to provide greater study visit scheduling flexibility for subjects and their guardians 6) Define Targeted Physical Exam 7) Change address of the PK analytical laboratory 8) Update serious adverse event contact information 9) Clarify reporting of suspected serious adverse events to relevant health authorities 10) Clarify inconsistencies within the protocol with respect to: pregnancy restrictions after study medication has been discontinued, endpoint definitions, efficacy analyses, and which concomitant medications are contraindicated 11) Correct typographical errors and administrative clarifications.
05 December 2008	To include information regarding the definition of a 'serious breach' of GCP, and to specify the associated reporting requirements including investigator reporting responsibilities.
18 October 2013	1. Address the potential safety issues associated with extreme elevations of ALT (serum ALT > 1,000 U/L or > 20x ULN and clinical or laboratory findings suggestive of liver dysfunction) due to acute exacerbation of CHB by providing emergency access to study ETV ("rescue ETV") for subjects who cannot access acceptable alternative anti-HBV therapy; 2. Specify that rescue ETV would be provided by the sponsor at the request of a primary investigator and approval of the Central Medical Monitor; 3. Specify that rescue therapy provided by the sponsor would be ETV only, and would be provided for up to 96 consecutive weeks; 4. Specify that the management of extreme elevations of ALT are at the discretion of the primary investigator; 5. Clarify that non-serious adverse events should be documented for all LTFU subjects receiving rescue ETV; 6. Change the duration of study to, "5 years, or until the last study subject treated with rescue ETV for an extreme elevation of ALT completes 48-weeks of off-treatment follow-up; whichever is later"; 7. Specify that on-treatment efficacy endpoints are based on ETV therapy, and therefore exclude rescue ETV; 8. Specify entecavir tablets should be protected from light during storage; 9. Modify Figure 5.3.2.1-1 to provide guidance to investigators managing significant elevations of ALT due to acute exacerbation of CHB.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported