Clinical trial results:
A Comparative Study of the Antiviral Efficacy and Safety of Entecavir (ETV) versus Placebo in Pediatric Subjects with Chronic Hepatitis B Virus (HBV) Infection who are HBeAg-Positive

Summary

EudraCT number	2009-016357-17
Trial protocol	DE GB GR BE Outside EU/EEA
Global end of trial date	03 April 2018

Results information

Result version number	v1 (current)
This version publication date	20 October 2018
First version publication date	20 October 2018

Trial information

Trial identification

Sponsor protocol code	AI463-189 ST

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01079806
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	Bristol-Myers Squibb International, EU Study Start-Up Unit, 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)	EMEA-000339-PIP02-03
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	03 April 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 April 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary study objective was to compare the proportion of subjects in each treatment group who demonstrated the combination of HBV deoxyribonucleic acid (DNA) viral suppression (< 50 IU/mL) and HBeAg seroconversion (undetectable HBeAg and detectable anti-HBe antibody [HBeAb]) at Week 48.

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	07 July 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 10
Country: Number of subjects enrolled	Romania: 19
Country: Number of subjects enrolled	Argentina: 1
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	Germany: 12
Country: Number of subjects enrolled	Greece: 1
Country: Number of subjects enrolled	India: 3
Country: Number of subjects enrolled	Israel: 11
Country: Number of subjects enrolled	Korea, Republic of: 23
Country: Number of subjects enrolled	Russian Federation: 19
Country: Number of subjects enrolled	Taiwan: 12
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	United States: 48
Worldwide total number of subjects	180
EEA total number of subjects	56

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)	87
Adolescents (12-17 years)	93
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Of 228 patients enrolled, 43 no longer met study criteria, 4 withdrew consent, and 1 withdrew for surgery. While the primary endpoint analysis was based on a randomized sample size of 123 participants, the overall study population was augmented to 180 to meet global regulatory requirements. All 180 randomized patients received study drug.

Period 1

Period 1 title	Day 1 to Week 96
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Entecavir

Arm description:

Participants received entecavir, 0.015 mg/kg up to 0.5 mg, once daily, for 96 to 144 weeks, depending on response.

Arm type	Experimental
Investigational medicinal product name	Entecavir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Soluble tablet, Tablet
Routes of administration	Oral use

Dosage and administration details:

Entecavir was dosed at 0.015 mg/kg/day up to a maximum dose of 0.5 mg/day using oral solution or tablets.

Arm title	Placebo

Arm description:

Participants received placebo, 0 mg, once daily, for 48 to 96 weeks, depending on response

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Soluble tablet, Tablet
Routes of administration	Oral use

Dosage and administration details:

Matching Placebo administered using oral solution or tablets

Number of subjects in period 1	Entecavir	Placebo
Started	120	60
Received treatment	120	60
Completed	113	53
Not completed	7	7
Consent withdrawn by subject	3	2
Adverse event, non-fatal	-	3
Subject request to stop study treatment	1	-
Pregnancy	-	1
Poor compliance or noncompliance	2	-
Lost to follow-up	1	-
Removal by Medical Monitor	-	1

Period 2

Period 2 title	Long-term Follow-up: Day 1-End of study
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	No
Arm title	Entecavir

Arm description:

Participants received entecavir, 0.015 mg/kg up to 0.5 mg, once daily, for 96 to 144 weeks, depending on response.

Arm type	Experimental
Investigational medicinal product name	Entecavir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet, Soluble tablet
Routes of administration	Oral use

Dosage and administration details:

Entecavir was dosed at 0.015 mg/kg/day up to a maximum dose of 0.5 mg/day using oral solution or tablets.

Arm title	Placebo

Arm description:

Participants received placebo, 0 mg, once daily, for 48 to 96 weeks, depending on response

Arm type	Placebo

Investigational medicinal product name	Entecavir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet, Soluble tablet
Routes of administration	Oral use

Dosage and administration details:

Entecavir was dosed at 0.015 mg/kg/day up to a maximum dose of 0.5 mg/day using oral solution or tablets.

Number of subjects in period 2	Entecavir	Placebo
Started	111	58
Completed	92	43
Not completed	19	15
Investigator Left Institution	-	1
Consent withdrawn by subject	13	8
Lost to follow-up	6	6

Baseline characteristics

Reporting groups	
Reporting group title	Entecavir
Reporting group description:	
Participants received entecavir, 0.015 mg/kg up to 0.5 mg, once daily, for 96 to 144 weeks, depending on response.	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo, 0 mg, once daily, for 48 to 96 weeks, depending on response	

Reporting group values	Entecavir	Placebo	Total
Number of subjects	120	60	180
Age, Customized Units: Subjects			
>=2 years to <=6 years|	27	14	41
>6 years to <=12 years|	31	15	46
>12 years to <18 years|	62	31	93
Age Continuous Units: Years			
arithmetic mean	10.5	10.8	
standard deviation	± 4.87	± 4.82	-
Sex: Female, Male Units: Subjects			
Female	42	29	71
Male	78	31	109
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	2	0	2
Not Hispanic or Latino	48	21	69
Unknown or Not Reported	70	39	109
Race/Ethnicity, Customized Units: Subjects			
Asian|	57	30	87
Black/African American|	14	2	16
Native Hawaiian/Other Pacific Islander|	1	0	1
White|	44	27	71
Other|	4	1	5

End points

End points reporting groups

Reporting group title	Entecavir
Reporting group description:	
Participants received entecavir, 0.015 mg/kg up to 0.5 mg, once daily, for 96 to 144 weeks, depending on response.	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo, 0 mg, once daily, for 48 to 96 weeks, depending on response	
Reporting group title	Entecavir
Reporting group description:	
Participants received entecavir, 0.015 mg/kg up to 0.5 mg, once daily, for 96 to 144 weeks, depending on response.	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo, 0 mg, once daily, for 48 to 96 weeks, depending on response	
Subject analysis set title	Blinded and Open-Label (All ETV)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Randomized ETV subjects combined with PBO-randomized subjects who received open-label ETV	
Subject analysis set title	Blinded and Open-Label (All ETV)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All ETV group during long-term follow-up that show increased ALT (alanine aminotransferase)	

Primary: Percentage of Participants Who Achieved a Combination of Hepatitis B Virus (HBV) DNA Suppression and Hepatitis B e Antigen (HBeAg) Seroconversion at Week 48

End point title	Percentage of Participants Who Achieved a Combination of Hepatitis B Virus (HBV) DNA Suppression and Hepatitis B e Antigen (HBeAg) Seroconversion at Week 48
End point description:	
Suppression=HBV DNA<50 IU/mL (approximately 300 copies/mL) using the Roche COBAS TaqMan HBV Test for use with the High Pure System assay; seroconversion=undetectable HBeAg and detectable anti-hepatitis B e antibodies. While the analysis of the primary endpoint was based on a randomized sample size of 123 participants (the Primary Cohort), the size of the overall study population was augmented to 180 randomized participants to meet global regulatory requirements.	
End point type	Primary
End point timeframe:	
At Week 48	

End point values	Entecavir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	41		
Units: Percentage of participants				
number (not applicable)	24.4	2.4		

Statistical analyses

Statistical analysis title	Week 48 HBV DNA Suppression + HBeAg Seroconversion
Comparison groups	Entecavir v Placebo
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0049
Method	Normal approximation
Parameter estimate	Difference estimate
Point estimate	20.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	9.1
upper limit	31.4

Secondary: Percentage of Participants With Hepatitis B Virus (HBV) DNA <50 IU/mL at Week 48

End point title	Percentage of Participants With Hepatitis B Virus (HBV) DNA <50 IU/mL at Week 48

End point description:

While the analysis of the primary endpoint was based on a randomized sample size of 123 participants (the Primary Cohort), the size of the overall study population was augmented to 180 randomized participants to meet global regulatory requirements.

End point type	Secondary

End point timeframe:

At Week 48

End point values	Entecavir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	41		
Units: Percentage of participants				
number (not applicable)	46.3	2.4		

Statistical analyses

Statistical analysis title	Hepatitis B Virus (HBV) DNA <50 IU/mL at Week 48
Comparison groups	Entecavir v Placebo
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Normal approximation
Parameter estimate	Difference estimate
Point estimate	41.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	29.4
upper limit	54.2

Secondary: Percentage of Participants With Serum Alanine Aminotransferase ≤1*Upper Limit of Normal at Week 48

End point title	Percentage of Participants With Serum Alanine Aminotransferase ≤1*Upper Limit of Normal at Week 48

End point description:

While the analysis of the primary endpoint was based on a randomized sample size of 123 participants (the Primary Cohort), the size of the overall study population was augmented to 180 randomized participants to meet global regulatory requirements.

End point type	Secondary

End point timeframe:

At Week 48

End point values	Entecavir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	41		
Units: Percentage of participants				
number (not applicable)	67.1	22.0		

Statistical analyses

Statistical analysis title	Serum ALT ≤1*ULN at Week 48
Comparison groups	Entecavir v Placebo
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Normal approximation
Parameter estimate	Difference estimate
Point estimate	45.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	29.2
upper limit	61.2

Secondary: Percentage of Participants With Hepatitis B Virus DNA <Limit of Quantitation (LOQ) at Week 48

End point title	Percentage of Participants With Hepatitis B Virus DNA <Limit of Quantitation (LOQ) at Week 48

End point description:

LOQ=29 IU/mL. While the analysis of the primary endpoint was based on a randomized sample size of 123 participants (the Primary Cohort), the size of the overall study population was augmented to 180 randomized participants to meet global regulatory requirements.

End point type	Secondary

End point timeframe:

At Week 48

End point values	Entecavir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	41		
Units: Percentage of participants				
number (not applicable)	42.7	2.4		

Statistical analyses

Statistical analysis title	HBV DNA <Limit of Quantitation (LOQ) at Week 48
Comparison groups	Entecavir v Placebo
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Normal approximation
Parameter estimate	Difference estimate
Point estimate	38.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	25.9
upper limit	50.5

Secondary: Percentage of Participants With Hepatitis B e Antigen (HBeAg)

Seroconversion at Week 48 (undetectable HBeAg and presence of anti-HBeAb)	
End point title	Percentage of Participants With Hepatitis B e Antigen (HBeAg) Seroconversion at Week 48 (undetectable HBeAg and presence of anti-HBeAb)

End point description:

HBe seroconversion=undetectable HBe antigen and detectable anti-HBe antibodies. While the analysis of the primary endpoint was based on a randomized sample size of 123 participants (the Primary Cohort), the size of the overall study population was augmented to 180 randomized participants to meet global regulatory requirements.

End point type	Secondary

End point timeframe:

At Week 48

End point values	Entecavir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	41		
Units: Percentage of participants				
number (not applicable)	24.4	12.2		

Statistical analyses

Statistical analysis title	HBeAg) Seroconversion at Week 48
Comparison groups	Entecavir v Placebo
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.11
Method	Normal approximation
Parameter estimate	Difference estimate
Point estimate	12.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	25.7

Secondary: Percentage of participants who achieved sustained HBeAg seroconversion during off-treatment follow up among participants who achieved HBeAg seroconversion at end of treatment.	
End point title	Percentage of participants who achieved sustained HBeAg seroconversion during off-treatment follow up among participants who achieved HBeAg seroconversion at end of treatment.

End point description:

Participants who demonstrated HBeAg seroconversion at EOD (end-of-dosing) were followed and assessed for presence of sustained HBeAg seroconversion during entire study. The study reached the

end of dosing (EOD) on 22 Feb-2016.

End point type	Secondary

End point timeframe:

Off-treatment follow-up

End point values	Entecavir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	22		
Units: Percentage of participants				
number (not applicable)				
EOD (end of dosing)|	100.0	100.0		
Week 48|	74.4	59.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with adverse events (including palatability issues), SAEs, discontinuous due to adverse events, and HBV disease progression through Week 48

End point title	Number of participants with adverse events (including palatability issues), SAEs, discontinuous due to adverse events, and HBV disease progression through Week 48

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. Related=having certain, probable, possible, or unknown relationship to study drug. Grade 1=Mild, Grade 2=Moderate, Grade 3=Severe, Grade 4=Life-threatening or disabling, Grade 5=Death. ALT=alanine aminotransferase.

End point type	Secondary

End point timeframe:

Day 1 through Week 48 on blinded therapy

End point values	Entecavir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	60		
Units: participants				
number (not applicable)				
Deaths|	0	0		
Serious Adverse Events|	4	7		
Discontinuation due to Adverse Event|	0	2		
any adverse event|	78	46		
Related Adverse Events|	11	6		

Related Grade 2 - 4 Adverse Events|	4	2		
Grade 3 - 4 Adverse Events|	4	3		
ALT Flares|	2	5		
HBV disease progression|	0	0		
Malignant neoplasms or pre-malignant lesions|	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Laboratory Test Results Meeting the Criteria for Abnormality (Grades 1-4)

End point title	Number of Participants With Laboratory Test Results Meeting the Criteria for Abnormality (Grades 1-4)

End point description:

Toxicities graded per Division of AIDS criteria, Version 1.0, and modified World Health Organization criteria. INR=international normalization ratio of prothrombin time; ULN=upper limit of normal. Hemoglobin (g/dL): Grade 1=10-10.9; Grade 2=9-9.9; Grade 3=7-8.9; Grade 4= <7. Platelets (/mm^3): Grade 1=100,000-124,999; Grade 2=50,000-99,999; Grade 3=25,000-49,999; Grade 4= <25,000. INR (*ULN): Grade 1=1.1-1.5; Grade 2=1.6-2; Grade 3=2.1-3; Grade 4= >3. WBC (/mm^3): Grade 1=2000-2500; Grade 2=1500-1999; Grade 3=1000-1499; Grade 4= <1000. Neutrophils (/mm^3): Grade 1=1000-1300; Grade 2=750-999; Grade 3=500-749; Grade 4= <500.

End point type	Secondary

End point timeframe:

Day 1 through Week 48 on blinded therapy

End point values	Entecavir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	60		
Units: Participants				
number (not applicable)				
Hemoglobin|	5	4		
Platelets|	3	2		
INR|	2	6		
White blood cells (WBC)|	2	1		
Neutrophils + bands (absolute)|	14	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Laboratory Test Results Meeting the Criteria for Abnormality (Grades 1-4) (Continued)

End point title	Number of Participants With Laboratory Test Results Meeting the Criteria for Abnormality (Grades 1-4) (Continued)

End point description:

Toxicities graded per Division of AIDS criteria, Version 1.0, and modified World Health Organization criteria. ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; ULN=upper limit of normal; LLN=lower limit of normal. ALT, AST (*ULN): Grade 1=1.25-2; Grade 2=2.6-5; Grade 3=5.1-10; Grade 4 => 10. Bilirubin (*ULN): Grade 1 = 1.1-1.5; Grade 2=1.6-2.5; Grade 3 = 2.6-5; Grade 4= >5. Albumin (g/dL): Grade 1=3- <LLN; Grade 2=2-2.9; Grade 3= <2. Lipase (*ULN): Grade 1=1.1-1.5; Grade 2=1.6-3; Grade 3=3.1-5; Grade 4= >5. BUN/urea (*ULN): Grade 1=1.25-<2.6; Grade 2=2.6-<5.1; Grade 3=5.1-10; Grade 4= >10. Chloride, high (mEq/L): Grade 1=113-<117; Grade 2=117-<121; Grade 3=121-125; Grade 4= >125. Potassium, low (mEq/L): Grade 1=3-3.4; Grade 2=2.5-<3; Grade 3=2-<2.5; Grade 4=<2. Potassium, high (mEq/L): : Grade 1= 5.6-<6.1; Grade 2=6.1-<6.6; Grade 3=6.6-7; Grade 4= >7. Sodium, high (mEq/L): Grade 1=146<151; Grade 2=151-<155; Grade 3=155-<160; Grade 4= >=160.

End point type	Secondary

End point timeframe:

Day 1 through Week 48 on blinded therapy

End point values	Entecavir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	60		
Units: participants				
number (not applicable)				
ALT|	113	59		
AST|	87	51		
Total bilirubin|	5	6		
Albumin|	0	1		
Lipase|	38	20		
BUN/Urea|	10	2		
Chloride, high|	2	1		
Potassium, low|	1	1		
Potassium, high|	1	0		
Sodium, high|	8	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With HBeAg Seroconversion on ETV over-time at Week 96 (All ETV cohort)

End point title	Percentage of Participants With HBeAg Seroconversion on ETV over-time at Week 96 (All ETV cohort)

End point description:

HBe seroconversion=undetectable HBe antigen and detectable anti-HBe antibodies. While the analysis of the primary endpoint was based on a randomized sample size of 123 participants (the Primary Cohort), the size of the overall study population was augmented to 180 randomized participants to meet global regulatory requirements.

End point type	Secondary

End point timeframe:

At Week 96

End point values	Blinded and Open-Label (All ETV)			
Subject group type	Subject analysis set			
Number of subjects analysed	171			
Units: Percentage of participants				
number (not applicable)	38.6			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who maintained HBeAg seroconversion at Week 96 (end of blinded therapy) among participants with HBeAg seroconversion at Week 48

End point title	Percentage of participants who maintained HBeAg seroconversion at Week 96 (end of blinded therapy) among participants with HBeAg seroconversion at Week 48

End point description:

Participants who achieved HBeAg seroconversion by Week 48 and maintained seroconversion to week 96

End point type	Secondary

End point timeframe:

At Week 96

End point values	Entecavir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	60		
Units: Percentage of participants				
number (not applicable)				
Week 48|	24.2	10.0		
Week 96|	36.7	99999		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Death as Outcome, Serious Adverse Events (SAEs), Discontinuations due to Adverse Events (AEs), Related AEs, Grade 2-4 Related AEs, Grade 3-4 AEs, Malignancies, ALT Flares, and Hepatic Disease Progression through week 96

End point title	Number of Participants With Death as Outcome, Serious Adverse Events (SAEs), Discontinuations due to Adverse Events

	(AEs), Related AEs, Grade 2-4 Related AEs, Grade 3-4 AEs, Malignancies, ALT Flares, and Hepatic Disease Progression through week 96

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. Related=having certain, probable, possible, or unknown relationship to study drug. Grade 1=Mild, Grade 2=Moderate, Grade 3=Severe, Grade 4=Life-threatening or disabling, Grade 5=Death. ALT=alanine aminotransferase.

End point type	Secondary

End point timeframe:

Day 1 through Week 96

End point values	Blinded and Open-Label (All ETV)			
Subject group type	Subject analysis set			
Number of subjects analysed	171			
Units: Participants				
number (not applicable)				
Deaths|	0			
SAEs|	8			
Discontinuations due to AEs|	1			
Related AEs|	14			
Grade 2-4 Related AEs|	4			
Grade 3-4 AEs|	7			
Malignancies|	0			
ALT flares|	3			
Hepatic disease progression|	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with HBeAg seroconversion (undetectable HBeAg and presence of anti-HBeAb) up to Week 96

End point title	Percentage of participants with HBeAg seroconversion (undetectable HBeAg and presence of anti-HBeAb) up to Week 96

End point description:

On Treatment through week 96 - 2 year cohort NC = F: (The numerator was based on participants meeting the response criteria. The denominator was based on treated participants. Participants who had missing data at the analysis week were considered failures.)

End point type	Secondary

End point timeframe:

up to week 96

End point values	Entecavir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	60[1]		
Units: Percentage of participants				
number (not applicable)	40.8	99999		

Notes:

[1] - Analysis was not performed

Statistical analyses

No statistical analyses for this end point

Secondary: Histological analysis (percentage) among participants with available liver biopsy data

End point title	Histological analysis (percentage) among participants with available liver biopsy data

End point description:

Liver function test elevations and abnormalities on blinded and open-label ETV (the All ETV Safety Cohort). Participants who experienced elevation of alanine aminotransferase (ALT) greater than three times ETV (entecavir) baseline measure (Participants who displayed liver biopsy with ALT value greater than three times baseline.)

End point type	Secondary

End point timeframe:

Between weeks 48 and 96

End point values	Blinded and Open-Label (All ETV)			
Subject group type	Subject analysis set			
Number of subjects analysed	171			
Units: Percentage of participants				
number (not applicable)	5.9			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with HbeAg loss at weeks 48 and 96

End point title	Percentage of participants with HbeAg loss at weeks 48 and 96

End point description:

HBeAg Loss (NC = F and NC = M) - On Treatment through Week 96 - Year 2 Efficacy Cohort Non-Completer - Failure (NC=F): The numerator was based on participants meeting the response criteria. The denominator was based on treated participants. Participants who had missing data at the analysis week were considered failures. Non-Completer - Missing (NC=M): The numerator was based on participants meeting the response criteria. The denominator was based on participants with data at the

analysis week. Participants who had missing data at the analysis week were excluded.

End point type	Secondary

End point timeframe:

At 48 and 96 weeks

End point values	Entecavir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	60[2]		
Units: Percentage of participants				
number (not applicable)				
48 weeks|	25.0	10.0		
96 Weeks|	40.8	99999		

Notes:

[2] - Subjects without HBeAg seroconversion were switched to open-label ETV

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On-treatment non serious adverse events (NSAEs) and serious adverse events (SAEs) were reported with onset on or after the first dosing date and on or prior to the 96 weeks of study ETV therapy.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Entecavir (ETV)

Reporting group description:

Subjects received 0.015 milligram per kilogram per day (mg/kg/day) (up to a maximum dose of 0.5 mg/day) ETV oral solution or tablets, once daily (QD).

Reporting group title	Placebo

Reporting group description:

Subjects received ETV matched placebo oral solution or tablets, QD.

Serious adverse events	Entecavir (ETV)	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 120 (3.33%)	9 / 60 (15.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Congenital, familial and genetic disorders			
Hydrocele			
subjects affected / exposed	1 / 120 (0.83%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	0 / 120 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inflammatory bowel disease			
subjects affected / exposed	0 / 120 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			

Hepatic function abnormal			
subjects affected / exposed	0 / 120 (0.00%)	2 / 60 (3.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Tonsillar hypertrophy			
subjects affected / exposed	1 / 120 (0.83%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	1 / 120 (0.83%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Schizophrenia			
subjects affected / exposed	0 / 120 (0.00%)	1 / 60 (1.67%)	
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			
Juvenile idiopathic arthritis			
subjects affected / exposed	0 / 120 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	0 / 120 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 120 (0.83%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			

subjects affected / exposed	0 / 120 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear infection			
subjects affected / exposed	1 / 120 (0.83%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic hepatitis b			
subjects affected / exposed	0 / 120 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious colitis			
subjects affected / exposed	0 / 120 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	0 / 120 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastoiditis			
subjects affected / exposed	0 / 120 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	0 / 120 (0.00%)	1 / 60 (1.67%)	
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: 5 %

Non-serious adverse events	Entecavir (ETV)	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	95 / 120 (79.17%)	53 / 60 (88.33%)	
Nervous system disorders			
Headache			
subjects affected / exposed	18 / 120 (15.00%)	9 / 60 (15.00%)	
occurrences (all)	24	55	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	18 / 120 (15.00%)	10 / 60 (16.67%)	
occurrences (all)	29	18	
Fatigue			
subjects affected / exposed	3 / 120 (2.50%)	5 / 60 (8.33%)	
occurrences (all)	3	5	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	5 / 120 (4.17%)	3 / 60 (5.00%)	
occurrences (all)	10	13	
Diarrhoea			
subjects affected / exposed	7 / 120 (5.83%)	7 / 60 (11.67%)	
occurrences (all)	8	16	
Abdominal pain			
subjects affected / exposed	9 / 120 (7.50%)	9 / 60 (15.00%)	
occurrences (all)	16	14	
Dyspepsia			
subjects affected / exposed	0 / 120 (0.00%)	4 / 60 (6.67%)	
occurrences (all)	0	6	
Nausea			
subjects affected / exposed	6 / 120 (5.00%)	5 / 60 (8.33%)	
occurrences (all)	6	6	
Vomiting			
subjects affected / exposed	14 / 120 (11.67%)	10 / 60 (16.67%)	
occurrences (all)	17	12	
Respiratory, thoracic and mediastinal disorders			
Cough			

subjects affected / exposed	15 / 120 (12.50%)	12 / 60 (20.00%)	
occurrences (all)	18	21	
Epistaxis			
subjects affected / exposed	8 / 120 (6.67%)	3 / 60 (5.00%)	
occurrences (all)	17	5	
Oropharyngeal pain			
subjects affected / exposed	7 / 120 (5.83%)	5 / 60 (8.33%)	
occurrences (all)	8	9	
Rhinitis allergic			
subjects affected / exposed	5 / 120 (4.17%)	3 / 60 (5.00%)	
occurrences (all)	7	4	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 120 (0.83%)	5 / 60 (8.33%)	
occurrences (all)	1	5	
Acne			
subjects affected / exposed	3 / 120 (2.50%)	3 / 60 (5.00%)	
occurrences (all)	4	3	
Urticaria			
subjects affected / exposed	2 / 120 (1.67%)	3 / 60 (5.00%)	
occurrences (all)	2	4	
Rash			
subjects affected / exposed	7 / 120 (5.83%)	2 / 60 (3.33%)	
occurrences (all)	8	3	
Infections and infestations			
Bronchitis			
subjects affected / exposed	8 / 120 (6.67%)	6 / 60 (10.00%)	
occurrences (all)	9	9	
Gastroenteritis			
subjects affected / exposed	6 / 120 (5.00%)	4 / 60 (6.67%)	
occurrences (all)	9	4	
Ear infection			
subjects affected / exposed	7 / 120 (5.83%)	1 / 60 (1.67%)	
occurrences (all)	7	2	
Influenza			

subjects affected / exposed	6 / 120 (5.00%)	4 / 60 (6.67%)	
occurrences (all)	6	4	
Pharyngitis			
subjects affected / exposed	5 / 120 (4.17%)	11 / 60 (18.33%)	
occurrences (all)	6	16	
Pharyngitis streptococcal			
subjects affected / exposed	4 / 120 (3.33%)	4 / 60 (6.67%)	
occurrences (all)	4	4	
Nasopharyngitis			
subjects affected / exposed	18 / 120 (15.00%)	14 / 60 (23.33%)	
occurrences (all)	28	26	
Pneumonia			
subjects affected / exposed	6 / 120 (5.00%)	0 / 60 (0.00%)	
occurrences (all)	10	0	
Upper respiratory tract infection			
subjects affected / exposed	19 / 120 (15.83%)	12 / 60 (20.00%)	
occurrences (all)	61	45	
Tonsillitis			
subjects affected / exposed	6 / 120 (5.00%)	1 / 60 (1.67%)	
occurrences (all)	6	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 September 2010	1) Augment the number of randomized subjects from 123 to 180 and increase the estimated number of participating study centers; 2) Change the entry ALT entry criteria from => 1.3 to => 1.5 x upper limit of normal (ULN), increase the minimum time span between the 2 pre-randomization ALT measurements from 4 to 8 weeks, and exclude other reasons for elevated ALT; 3) Specify the early unblinding and mechanism for doing so if subjects demonstrate significant worsening of HBV clinical symptoms or increases in ALT; 4) Specify additional analyses that will be conducted as key secondary and exploratory endpoints; 5) Modify the blood volume collected at some visits due to minimum fill volume requirements of available specimen collection tubes; 6) Summarize the plan for PK/PD analyses that will integrate Studies AI463028 and AI463189.
04 September 2012	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 open-label study ETV ("rescue open-label ETV") for subjects who cannot access acceptable alternative anti-HBV therapy. 1) Specify that rescue open-label ETV would be provided by the sponsor at the request of a primary investigator and approval of the Central Medical Monitor; 2) Specify that rescue therapy provided by the sponsor would be open-label ETV only, and would be provided for up to 96 consecutive weeks; 3) Specify that the management of extreme elevations of ALT are at the discretion of the primary investigator; 4) Clarify that non-serious adverse events should be documented for all LTFU subjects receiving rescue open-label ETV; 5) Change the duration of study to, "5 years, or until the last study subject treated with rescue open-label ETV for an extreme elevation of ALT completes 48-weeks of off-treatment follow-up; whichever is later"; 6) Specify that on-treatment efficacy endpoints are based on double-blind or open-label ETV therapy, and therefore exclude rescue open-label ETV: 7) Modify Figure 5.3.2.1 to provide guidance to investigators managing significant

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported