Clinical trial results:
A Study of the Safety and Efficacy of Entecavir plus Tenofovir in Adults with Chronic Hepatitis B Virus Infection with Previous Nucleoside/Nucleotide Treatment Failure

Summary

EudraCT number	2009-015705-40
Trial protocol	NL IT DE FR
Global end of trial date	18 February 2014

Results information

Result version number	v1 (current)
This version publication date	01 April 2016
First version publication date	01 April 2016

Trial information

Trial identification

Sponsor protocol code	AI463-203

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01063036
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Bristol-Myers Squibb International Corporation, Chaussée de la Hulpe 185, Brussels, Belgium, 1170
Public contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, 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)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 February 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 February 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to describe the efficacy of the combination therapy of Entecavir plus Tenofovir Disoproxil Fumarate at 48 weeks of treatment, in control of viral load Hepatitis B Virus (HBV) DNA <50 IU/mL in chronic HBV infected subjects who have failed previous treatment.

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	17 May 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 9
Country: Number of subjects enrolled	Poland: 43
Country: Number of subjects enrolled	Romania: 30
Country: Number of subjects enrolled	France: 16
Country: Number of subjects enrolled	Germany: 43
Country: Number of subjects enrolled	Italy: 3
Worldwide total number of subjects	144
EEA total number of subjects	144

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	129
From 65 to 84 years	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study initiated 17 May 2010; Week 48 Primary Endpoint 27 November 2012; Week 96 Study Completed 18 February 2014. Subjects with chronic Hepatitis B with surface antigen who have been currently treated and experienced treatment failure were enrolled.

Pre-assignment

Screening details:

144 enrolled; 92 treated. Reasons for 52 never treated: physical/laboratory test findings 30; not in target population 21; no signed consent 7; medical history/concurrent disease 2; other exclusion criteria 1; unknown 3.

Period 1

Period 1 title	Subjects Treated With Study Drug
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Entecavir + Tenofovir

Arm description:

Entecavir: Tablets, Oral, 1 mg, once daily, 96 weeks.

Tenofovir disoproxil fumarate: Tablets, Oral, 300 mg, once daily, 96 weeks.

Arm type	Experimental
Investigational medicinal product name	Entecavir
Investigational medicinal product code	BMS-200475
Other name	Baraclude®
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Entecavir: Tablets, Oral, 1 mg, once daily, 96 weeks.

Investigational medicinal product name	Tenofovir
Investigational medicinal product code	
Other name	Viread®
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Tenofovir disoproxil fumarate: Tablets, Oral, 300 mg, once daily, 96 weeks.

Number of subjects in period 1[1]	Entecavir + Tenofovir
Started	92
Completed	86
Not completed	6
Consent withdrawn by subject	2
Adverse event, non-fatal	1

Pregnancy	1
Lost to follow-up	1
Protocol deviation	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Out of the 144 enrolled, only 92 subjects were treated. Reasons for 52 never treated: physical/laboratory test findings 30; not in target population 21; no signed consent 7; medical history/concurrent disease 2; other exclusion criteria 1; unknown 3. Few subjects had more than one reason for not being treated.

Period 2

Period 2 title	Post Dosing Follow-up Through 24 Weeks
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Entecavir + Tenofovir

Arm description:

Entecavir: Tablets, Oral, 1 mg, once daily, 96 weeks.

Tenofovir disoproxil fumarate: Tablets, Oral, 300 mg, once daily, 96 weeks.

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

Dosage and administration details:

Entecavir: Tablets, Oral, 1 mg, once daily, 96 weeks.

Investigational medicinal product name	Tenofovir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Tenofovir disoproxil fumarate: Tablets, Oral, 300 mg, once daily, 96 weeks.

Number of subjects in period 2[2]	Entecavir + Tenofovir
Started	85
Completed	46
Not completed	39
Consent withdrawn by subject	6
Other	32
Lost to follow-up	1

Notes:

[2] - 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: Of the 86 subjects who completed treatment, 3 subjects were lost to follow-up, but 2 subjects who did not complete treatment went into the post-dosing phase, bringing the total entering follow-up to 85 subjects.

Baseline characteristics

Reporting groups	
Reporting group title	Entecavir + Tenofovir
Reporting group description:	
Entecavir: Tablets, Oral, 1 mg, once daily, 96 weeks.	
Tenofovir disoproxil fumarate: Tablets, Oral, 300 mg, once daily, 96 weeks.	

Reporting group values	Entecavir + Tenofovir	Total	
Number of subjects	92	92	
Age categorical Units: Subjects			
Adults (18-64 years)	81	81	
From 65-84 years	11	11	
Age continuous Units: years			
median	42.5		
full range (min-max)	19 to 85	-	
Gender categorical Units: Subjects			
Female	23	23	
Male	69	69	
Baseline Hepatitis B e Antigen Units: Subjects			
Positive for Hepatitis B e antigen	56	56	
Negative for Hepatitis B e antigen	34	34	
Missing Hepatitis B e antigen test	2	2	
Baseline Hepatitis B e Antibody Units: Subjects			
Positive for Hepatitis B e antibody	32	32	
Negative for Hepatitis B e antibody	56	56	
Intermediate Hepatitis B e antibody	2	2	
Missing Hepatitis B e antibody test	2	2	
Baseline Hepatitis B Surface Antigen Units: Subjects			
Positive for Hepatitis B Surface Antigen	92	92	
Negative for Hepatitis B Surface Antigen	0	0	
Baseline HBV Subtype Units: Subjects			
HBV Subtype A	21	21	
HBV Subtype B	2	2	
HBV Subtype C	1	1	
HBV Subtype D	35	35	
HBV Subtype E	4	4	
HBV Subtype G	1	1	
HBV Subtype H	1	1	
HBV Subtype Indeterminate	3	3	

Insufficient HBV DNA	23	23	
Missing HBV DNA test	1	1	
Prior Treatment Failure Units: Subjects			
Primary Non-Response	9	9	
Virological Breakthrough	30	30	
Partial Virological Breakthrough	52	52	
Missing	1	1	
HBV DNA by PCR (log10 IU/mL)			
Hepatitis B virus DNA (HBV DNA) by polymerase chain reaction was measured using the Roche COBAS(REGISTERED) TaqMan - High Pure System assay. The results were reported in IU/mL, with the limit of quantification (LOQ) = 29 IU/mL and lower limit of detection = 6 IU/mL. HBV DNA measurements were transformed by the log10, using log10(LOQ-1) for values below LOQ.			
Units: log10 IU/mL			
median	3.674		
full range (min-max)	1.45 to 9.3	-	

End points

End points reporting groups

Reporting group title	Entecavir + Tenofovir

Reporting group description:

Entecavir: Tablets, Oral, 1 mg, once daily, 96 weeks.

Tenofovir disoproxil fumarate: Tablets, Oral, 300 mg, once daily, 96 weeks.

Reporting group title	Entecavir + Tenofovir

Reporting group description:

Entecavir: Tablets, Oral, 1 mg, once daily, 96 weeks.

Tenofovir disoproxil fumarate: Tablets, Oral, 300 mg, once daily, 96 weeks.

Primary: Percentage of Subjects With a Virologic Response at Week 48 - Treated Population

End point title	Percentage of Subjects With a Virologic Response at Week 48 - Treated Population[1]

End point description:

Virologic response was defined as Hepatitis B virus (HBV) DNA <50 IU/mL; approximately 300 copies/mL. Percentage was calculated using non-completer=failure, defined as the number of subjects with virologic response at Week 48 divided by the number of treated subjects. An exact binomial 95% confidence interval was constructed. HBV DNA by polymerase chain reaction was measured in using the Roche COBAS(REGISTERED) TaqMan - High Pure System assay in IU/mL, with the limit of quantification=29 IU/mL and lower limit of detection=6 IU/mL. All treated subjects were analyzed.

End point type	Primary

End point timeframe:

Week 48

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: This is a single-arm estimation study in which the primary end point is assessed with proportions.

End point values	Entecavir + Tenofovir			
Subject group type	Reporting group			
Number of subjects analysed	92			
Units: percentage of subjects				
number (confidence interval 95%)	76.1 (66.1 to 84.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With a Virologic Response at Week 24 and at Week 96 - Treated Population

End point title	Percentage of Subjects With a Virologic Response at Week 24 and at Week 96 - Treated Population

End point description:

Virologic response was defined as Hepatitis B virus (HBV) DNA <50 IU/mL; approximately 300 copies/mL. Percentage was calculated using non-completer=failure, defined as the number of subjects with virologic response at Week 24, Week 96 divided by the number of treated subjects. An exact binomial 95% confidence interval was constructed. HBV DNA by polymerase chain reaction was measured using the Roche COBAS(REGISTERED) TaqMan - High Pure System assay in IU/mL, with the limit of quantification=29 IU/mL and lower limit of detection=6 IU/mL. All treated subjects were analyzed.

End point type	Secondary

End point timeframe:

Week 24, Week 96

End point values	Entecavir + Tenofovir			
Subject group type	Reporting group			
Number of subjects analysed	92			
Units: percentage of subjects				
number (confidence interval 95%)				
Week 24 (n=92)	64.1 (53.5 to 73.9)			
Week 96 (n=92)	84.8 (75.8 to 91.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Mean log10 Hepatitis B Virus DNA at Weeks 12, 24, 48, and 96 - Treated Evaluable Population

End point title	Change From Baseline in Mean log10 Hepatitis B Virus DNA at Weeks 12, 24, 48, and 96 - Treated Evaluable Population

End point description:

Hepatitis B Virus (HBV) DNA by polymerase chain reaction was measured in IU/mL using the Roche COBAS(REGISTERED) TaqMan - High Pure System assay, with the limit of quantification (LOQ)=29 IU/mL and lower limit of detection=6 IU/mL. HBV DNA measurements were transformed by log10, using log10(LOQ-1) for values below LOQ. Baseline was last measurement before or on Day 1 of study drug. All treated subjects with results at both baseline and on-treatment were analyzed. n=number of treated subjects with results at baseline and Week 12, Week 24, Week 48 and Week 96.

End point type	Secondary

End point timeframe:

Baseline to Weeks 12, 24, 48, 96

End point values	Entecavir + Tenofovir			
Subject group type	Reporting group			
Number of subjects analysed	89			
Units: log10 IU/mL				
arithmetic mean (standard deviation)				
Week 12 (n=89)	-2.23 (± 1.5339)			
Week 24 (n=89)	-2.581 (± 1.8019)			
Week 48 (n=88)	-2.829 (± 2.0537)			
Week 96 (n=84)	-2.965 (± 2.1431)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Hepatitis B Virus DNA Less Than the Lower Limit of Detection (LLD) at Weeks 24, 48, and 96 - Treated Population

End point title	Percentage of Subjects With Hepatitis B Virus DNA Less Than the Lower Limit of Detection (LLD) at Weeks 24, 48, and 96 - Treated Population

End point description:

HBV DNA <LLD (6 IU/mL) was defined/measured by the COBAS (REGISTERED) TaqMan High Pure System assay at Weeks 24, 48, and 96. Percentage was calculated using non-completer=failure, defined as number of subjects with HBV DNA <LLD at Weeks 24, 48, 96 divided by the number of treated subjects. An exact binomial 95% confidence interval was constructed. All treated subjects were analyzed.

End point type	Secondary

End point timeframe:

Weeks 24, 48, 96

End point values	Entecavir + Tenofovir			
Subject group type	Reporting group			
Number of subjects analysed	92			
Units: percentage of subjects				
number (confidence interval 95%)				
Week 24 (n=92)	12 (6.1 to 20.4)			
Week 48 (n=92)	18.5 (11.1 to 27.9)			
Week 96 (n=92)	16.3 (9.4 to 25.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Hepatitis B e Antigen (HBeAg) Loss at Weeks 24, 48, and 96 - Treated Population Who Were HBeAg Positive at Baseline

End point title	Percentage of Subjects With Hepatitis B e Antigen (HBeAg) Loss at Weeks 24, 48, and 96 - Treated Population Who Were HBeAg Positive at Baseline

End point description:

Loss of HBeAg was defined as being HBeAg-negative at Weeks 24, 48, and 96 in those subjects who had been HBeAg-positive at baseline. Method used for HBeAg was DiaSorin - Anti HBe enzyme immunoassay kit – procedure for qualitative determination of antibodies to HBeAg in human serum or plasma samples. Percentage was calculated using non-completer=failure, defined as number of subjects with HBeAg loss at Weeks 24 and 48 divided by the number of treated subjects who were HBeAg-positive at baseline. An exact binomial 95% confidence interval was constructed. Baseline was the last measurement before or on Day 1 of study drug. All treated subjects who were HBeAg-positive at baseline were analyzed.

End point type	Secondary

End point timeframe:

Baseline to Weeks 24, 48, and 96

End point values	Entecavir + Tenofovir			
Subject group type	Reporting group			
Number of subjects analysed	56			
Units: percentage of subjects				
number (confidence interval 95%)				
Week 24 (n=56)	3.6 (0.4 to 12.3)			
Week 48 (n=56)	5.46 (1.1 to 14.9)			
Week 96 (n=56)	8.9 (3 to 19.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Hepatitis B e (HBe) Seroconversion at Weeks 24, 48, and 96 - Treated Population Who Were Hepatitis B e Antigen (HBeAg)-positive at Baseline

End point title	Percentage of Subjects With Hepatitis B e (HBe) Seroconversion at Weeks 24, 48, and 96 - Treated Population Who Were Hepatitis B e Antigen (HBeAg)-positive at Baseline

End point description:

HBe seroconversion was defined as being both HBeAg-negative and Hepatitis B e antibody (HBeAb)-positive at Weeks 24, 48, and 96 in those subjects who had been HBeAg-positive at baseline. Method used was DiaSorin - Anti HBe enzyme immunoassay kit - procedure for qualitative determination of antibodies to HBeAg in human serum or plasma samples. Percentage was calculated using non-completer=failure, defined as number of subjects with HBe seroconversion at Weeks 24, 48, and 96 divided by the number of treated subjects who were HBeAg-positive at baseline. An exact binomial 95% confidence interval was constructed. Baseline was last measurement before or on Day 1 of study drug. All treated subjects who were HBeAg-positive at baseline were analyzed.

End point type	Secondary

End point timeframe:

Baseline, Weeks 24, 48, and 96

End point values	Entecavir + Tenofovir			
Subject group type	Reporting group			
Number of subjects analysed	56			
Units: percentage of subjects				
number (confidence interval 95%)				
Week 24 (n=56)	3.6 (0.4 to 12.3)			
Week 48 (n=56)	3.6 (0.4 to 12.3)			
Week 96 (n=56)	1.8 (0 to 9.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Hepatitis B Surface Antigen (HBsAg) Loss at Weeks 24, 48, 96 - Treated Population Who Were HBsAg-Positive at Baseline

End point title	Percentage of Subjects With Hepatitis B Surface Antigen (HBsAg) Loss at Weeks 24, 48, 96 - Treated Population Who Were HBsAg-Positive at Baseline

End point description:

Loss of HBsAg was defined as being HBsAg-negative at Weeks 24, 48, 96 in those subjects who had been HBsAg-positive at baseline. The method used: Immunoassay – ADVIA CENTAUR from SIEMENS: in vitro diagnostic immunoassay for the qualitative and quantitative determination of HBsAg in human serum and plasma (potassium ethylene diamine tetraacetic acid, lithium or sodium heparinized). Percentage was calculated using non-completer=failure, defined as number of subjects with a HBsAg loss at Weeks 24, 48, and 96 divided by the number of treated subjects who were HBsAg-positive at baseline (subjects were not enrolled into the study unless they were positive for HBsAg). An exact binomial 95% confidence interval was constructed. Baseline was last measurement before or on Day 1 of study drug. All treated subjects who were HBsAg-positive at baseline were analyzed.

End point type	Secondary

End point timeframe:

Baseline, Weeks 24, 48, 96

End point values	Entecavir + Tenofovir			
Subject group type	Reporting group			
Number of subjects analysed	92			
Units: percentage of subjects				
number (confidence interval 95%)				
Week 24 (n=92)	1.1 (0 to 5.9)			
Week 48 (n=92)	0 (0 to 0)			
Week 96 (n=92)	2.2 (0.3 to 7.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Hepatitis B Surface Antigen (HBsAg) Seroconversion at Weeks 24, 48, and 96 - Treated Population Who Were HBsAg-Positive at Baseline

End point title	Percentage of Subjects With Hepatitis B Surface Antigen (HBsAg) Seroconversion at Weeks 24, 48, and 96 - Treated Population Who Were HBsAg-Positive at Baseline

End point description:

HBsAg seroconversion was defined as being both HBsAg-negative and hepatitis B surface antibody (HBsAb)-positive at Weeks 24, 48, and 96 in those subjects who had been HBsAg-positive at baseline. The method used was an Immunoassay testing – ADVIA CENTAUR from SIEMENS: in vitro diagnostic immunoassay for the qualitative and quantitative determination of HBsAg in human serum and plasma [potassium ethylenediaminetetraacetic acid, lithium or sodium heparinized]. Percentage was calculated using non-completer=failure, defined as number of subjects with HBs seroconversion at Weeks 24 and 48 divided by the number of treated subjects who were HBsAg-positive at baseline. Positive result for HBsAg was one of the inclusion criteria. An exact binomial 95% confidence interval was constructed. Baseline was last measurement before or on Day 1 of study drug. All treated subjects who were HBsAg-positive at baseline were analyzed.

End point type	Secondary

End point timeframe:

Baseline, Weeks 24, 48, and 96

End point values	Entecavir + Tenofovir			
Subject group type	Reporting group			
Number of subjects analysed	92			
Units: percentage of subjects				
number (confidence interval 95%)				
Week 24 (n=92)	1.1 (0 to 5.9)			
Week 48 (n=92)	0 (0 to 0)			
Week 96 (n=92)	1.1 (0 to 5.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment Emergent Serious Adverse Events (SAEs) on Treatment, and Discontinuation of Study Drug Due to Adverse Events (AE) - Treated Population

End point title	Number of Subjects With Treatment Emergent Serious Adverse Events (SAEs) on Treatment, and Discontinuation of Study

	Drug Due to Adverse Events (AE) - Treated Population

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. Treatment-related=having certain, probable, possible, or missing relationship to study drug. Grade (Gr) 1=Mild, Gr 2=Moderate, Gr 3=Severe, Gr 4=Life-threatening or disabling. On-treatment = on Day 1 through last dose of study therapy + 5 days. All treated subjects were analyzed.

End point type	Secondary

End point timeframe:

Day 1 to last dose of study drug plus 5 days; up to Week 96

End point values	Entecavir + Tenofovir			
Subject group type	Reporting group			
Number of subjects analysed	92			
Units: subjects				
Treatment emergent SAE	6			
Discontinuation of treatment due to AE	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Emergence of Genotypic Resistance to Study Drugs at Weeks 48 and 96 - Treated Population

End point title	Number of Subjects With Emergence of Genotypic Resistance to Study Drugs at Weeks 48 and 96 - Treated Population

End point description:

Testing of Hepatitis B Virus (HBV) genotype was performed at baseline for all treated subjects and for subjects at Weeks 48 and 96 with primary non-response or virologic breakthrough. Emergent genotypic resistance to study drugs was defined as follows: Emergent=on-treatment substitution not present at baseline; entecavir resistance: subject's sample had rtM204V/I/S and any substitution at rtT184, rtS202, or rtM250; tenofovir resistance: subject's sample had rtA181T/V or rtN236T. Primary non-response was defined as <1 log10 decrease in HBV DNA from baseline on treatment at or after Week 12. Virologic breakthrough was defined as >=1 log10 increase in HBV DNA over nadir on treatment, either confirmed on treatment or last on-treatment followed by discontinuation of study therapy. n=number of subjects analyzed at Weeks 48 and 96.

End point type	Secondary

End point timeframe:

Baseline to Weeks 48, 96

End point values	Entecavir + Tenofovir			
Subject group type	Reporting group			
Number of subjects analysed	7[2]			
Units: subjects				
Week 48 (n=5)	0			
Week 96 (n=7)	0			

Notes:

[2] - Treated subjects who met resistance testing criteria; were tested for resistance to both drugs.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects on Treatment With Study Drug With Laboratory Test Abnormalities Meeting Selected Criteria on Treatment - Treated Population

End point title	Number of Subjects on Treatment With Study Drug With Laboratory Test Abnormalities Meeting Selected Criteria on Treatment - Treated Population

End point description:

Select laboratory abnormalities and elevations on treatment are presented in each category. Baseline (BL); alanine transaminase (ALT); Creatinine (Cr) data presented below were confirmed, that is, at least 2 sequential measurement or last on-treatment measurement meeting the elevation criteria. On-treatment=after Day 1 through last dose of study therapy + 5 days. n=treated subjects with on-treatment laboratory test results.

End point type	Secondary

End point timeframe:

Day 1 to last dose of study drug plus 5 days; up to Week 96

End point values	Entecavir + Tenofovir			
Subject group type	Reporting group			
Number of subjects analysed	91[3]			
Units: subjects				
ALT >2*Baseline(n=90)	9			
ALT >3*Baseline(n=90)	2			
Total bilirubin >2*Baseline (n=90)	11			
Total bilirubin >3*Baseline (n=90)	3			
Lipase >3*Baseline (n=90)	4			
Confirmed Cr increase from BL >=20% (n=91)	4			
Confirmed Cr >1.5 mg/dL (n=91)	2			
Confirmed Cr increase from BL >=0.3 mg/dL (n=91)	1			
Confirmed Cr increase from BL >=0.5 mg/dL (n=91)	1			
Cr clearance <50 mL/min (n=91)	1			
Phosphate <2.0 mg/dL (n=90)	2			
Phosphate <2.3 mg/dL (n=90)	8			

Notes:
[3] - Subjects who were evaluable for this end point.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Day 1 up to 96 Weeks	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups	
Reporting group title	Entecavir + Tenofovir
Reporting group description:	
Entecavir: Tablets, Oral, 1 mg, once daily, 96 weeks. Tenofovir disoproxil fumarate: Tablets, Oral, 300 mg, once daily, 96 weeks.	

Serious adverse events	Entecavir + Tenofovir		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 92 (6.52%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular carcinoma			
subjects affected / exposed	2 / 92 (2.17%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Radius fracture			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Cataract			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Inguinal hernia			

subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemorrhoids			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Entecavir + Tenofovir		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	42 / 92 (45.65%)		
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 92 (5.43%)		
occurrences (all)	7		
Headache			
subjects affected / exposed	6 / 92 (6.52%)		
occurrences (all)	7		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	6 / 92 (6.52%)		
occurrences (all)	6		
Fatigue			
subjects affected / exposed	9 / 92 (9.78%)		
occurrences (all)	9		
Gastrointestinal disorders			
Nausea			

subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Dyspepsia subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all)	8 / 92 (8.70%) 9 5 / 92 (5.43%) 5 7 / 92 (7.61%) 7 6 / 92 (6.52%) 6		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	7 / 92 (7.61%) 8		
Infections and infestations Bronchitis subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all)	6 / 92 (6.52%) 7 11 / 92 (11.96%) 12		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 December 2009	The purpose of this amendment was to provide protocol revisions in line with feedback received from the European Union Competent Authority and with the Summary of Product Characteristics for tenofovir.
18 January 2011	The purpose of this amendment was to: change the 24-hr Emergency Telephone Number; change the required number of enrolled and treated subjects, as well as the screening failure rate; replace, based on the current targeted number of treated subjects, the semi-width of the 95% confidence interval (CI) for a range of observed response rates, from 10% to 13.2%; change the number of subjects to be included in the interim analysis; clarify the sub-criteria for partial virological response; replace based on the current targeted number of treated subjects, the calculation of the 95% CI for the observed proportion from a 95% CI based on normal approximation into an exact binomial 95% CI; clarify the timing of the main (Week 48) and final (Week 96) analysis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported