Clinical trial results:
A Phase 3, Double-Blind, Randomized, Placebo-Controlled Study of the Safety and Efficacy of Adefovir Dipivoxil in Children and Adolescents (Age 2 to Less Than 18) With Chronic Hepatitis B

Summary

EudraCT number	2004-001346-33
Trial protocol	ES Outside EU/EEA
Global end of trial date	09 April 2010

Results information

Result version number	v1 (current)
This version publication date	22 March 2016
First version publication date	05 August 2015

Trial information

Trial identification

Sponsor protocol code	GS-US-103-0518

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00095121
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Gilead Sciences
Sponsor organisation address	Flowers Building, Granta Park, Abington, Cambridge, United Kingdom, CB21 6GT
Public contact	Clinical Trial Mailbox, Gilead Sciences International Ltd, ClinicalTrialDisclosures@gilead.com
Scientific contact	Clinical Trial Mailbox, Gilead Sciences International Ltd, ClinicalTrialDisclosures@gilead.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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 April 2010
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 April 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to investigate the efficacy and safety of adefovir dipivoxil (ADV) for the treatment of chronic hepatitis B in children and adolescents (age 2 to less than 18 years) following 48 weeks of placebo-controlled, double-blind treatment and following an additional 192 weeks of open-label ADV treatment.

Protection of trial subjects:

The protocol and consent/assent forms were submitted by each investigator to a duly constituted Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for review and approval before study initiation. All revisions to the consent/assent forms (if applicable) after initial IEC/IRB approval were submitted by the investigator to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements.

This study was conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 May 2004
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	Germany: 19
Country: Number of subjects enrolled	Poland: 75
Country: Number of subjects enrolled	United Kingdom: 14
Country: Number of subjects enrolled	Belgium: 9
Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	United States: 48
Worldwide total number of subjects	173
EEA total number of subjects	125

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)	90
Adolescents (12-17 years)	83
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first participant was screened on 17 May 2004. The last study visit occurred on 09 April 2010.

Pre-assignment

Screening details:

293 subjects were screened.

Period 1

Period 1 title	Overall study (overall period)
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	ADV - ADV

Arm description:

Participants were randomized to receive ADV in the double-blind period (up to 48 weeks) followed by ADV in the open-label period (up to an additional 192 weeks). Lamivudine was added to the open-label ADV regimen of subjects between 12 and < 18 years old who had prior lamivudine exposure and who had a serum HBV DNA concentration ≥ 1000 copies/mL at 2 consecutive study visits at or after Study Week 96.

Arm type	Experimental
Investigational medicinal product name	Adefovir dipivoxil
Investigational medicinal product code	
Other name	ADV, Hepsera®
Pharmaceutical forms	Oral suspension, Tablet
Routes of administration	Oral use

Dosage and administration details:

Children aged 2 to < 7 years received 0.3 mg/kg oral suspension; children aged ≥ 7 to < 12 years received 0.25 mg/kg oral suspension; children aged ≥ 12 to < 18 years received a 10 mg tablet.

Arm title	PLB - ADV

Arm description:

Participants were randomized to receive placebo (PLB) to match ADV in the double-blind period (up to 48 weeks) followed by ADV in the open-label period (up to an additional 192 weeks). Lamivudine was added to the open-label ADV regimen of subjects between 12 and < 18 years old who had prior lamivudine exposure and who had a serum HBV DNA concentration ≥ 1000 copies/mL at 2 consecutive study visits at or after Study Week 96.

Arm type	Experimental
Investigational medicinal product name	Placebo to match ADV
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet, Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Children aged 2 to < 12 years received placebo as an oral suspension; children aged ≥ 12 to < 18 years received placebo as a tablet.

Investigational medicinal product name	Adefovir dipivoxil
Investigational medicinal product code	
Other name	ADV, Hepsera®

Pharmaceutical forms	Oral suspension, Tablet
Routes of administration	Oral use

Dosage and administration details:

Children aged 2 to < 7 years received 0.3 mg/kg oral suspension; children aged ≥ 7 to < 12 years received 0.25 mg/kg oral suspension; children aged ≥ 12 to < 18 years received a 10 mg tablet.

Number of subjects in period 1	ADV - ADV	PLB - ADV
Started	115	58
Completed double-blind phase	112	58
Started open-label phase	108	54
Received lamivudine (LAM) after Week 96	21 [1]	11 [2]
Completed	46	35
Not completed	69	23
Adverse event, non-fatal	2	-
Did not enter open-label phase	4	4
Other	47	16
Progressive disease	2	1
Withdrew consent	6	-
Lost to follow-up	1	1
Participant noncompliance	7	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The milestones presented use the current functionality of the EU-CTR in order to best report the summary results in an informative way.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The milestones presented use the current functionality of the EU-CTR in order to best report the summary results in an informative way.

Baseline characteristics

Reporting groups	
Reporting group title	ADV - ADV
Reporting group description:	
Participants were randomized to receive ADV in the double-blind period (up to 48 weeks) followed by ADV in the open-label period (up to an additional 192 weeks). Lamivudine was added to the open-label ADV regimen of subjects between 12 and < 18 years old who had prior lamivudine exposure and who had a serum HBV DNA concentration ≥ 1000 copies/mL at 2 consecutive study visits at or after Study Week 96.	
Reporting group title	PLB - ADV
Reporting group description:	
Participants were randomized to receive placebo (PLB) to match ADV in the double-blind period (up to 48 weeks) followed by ADV in the open-label period (up to an additional 192 weeks). Lamivudine was added to the open-label ADV regimen of subjects between 12 and < 18 years old who had prior lamivudine exposure and who had a serum HBV DNA concentration ≥ 1000 copies/mL at 2 consecutive study visits at or after Study Week 96.	

Reporting group values	ADV - ADV	PLB - ADV	Total
Number of subjects	115	58	173
Age Categorical Units: participants			
Age Continuous Units: years			
arithmetic mean	10.8	10.7	
standard deviation	± 4.33	± 3.94	-
Gender, Male/Female Units: participants			
Female	41	19	60
Male	74	39	113
Ethnicity Units: Subjects			
Hispanic or Latino	1	0	1
Not Hispanic or Latino	114	58	172
Race Units: Subjects			
American Indian or Alaska Native	1	0	1
Asian	29	12	41
Black or African American	11	3	14
White	70	41	111
More than one race	4	2	6
Hepatitis B Surface Antigen (HBsAg) Units: Subjects			
Negative	0	0	0
Positive	115	58	173
Antibody to HBsAg (HBsAb) Units: Subjects			
Negative	0	0	0
Positive	0	0	0
Not Done	115	58	173

Hepatitis B e Antigen (HBeAg) Units: Subjects			
Negative	2	1	3
Positive	113	57	170
Antibody to HBeAg (HBeAb) Units: Subjects			
Negative	0	0	0
Positive	2	1	3
Not Done	113	57	170
Alanine aminotransferase (ALT) Normal Units: Subjects			
≥ upper limit of normal (ULN)	108	56	164
< ULN	7	2	9
HBV DNA Units: log10 copies/mL			
arithmetic mean	8.74	8.67	
standard deviation	± 0.894	± 1.016	-
ALT Units: U/L			
arithmetic mean	111	99	
standard deviation	± 81.6	± 52.8	-

End points

End points reporting groups

Reporting group title	ADV - ADV

Reporting group description:

Participants were randomized to receive ADV in the double-blind period (up to 48 weeks) followed by ADV in the open-label period (up to an additional 192 weeks). Lamivudine was added to the open-label ADV regimen of subjects between 12 and < 18 years old who had prior lamivudine exposure and who had a serum HBV DNA concentration ≥ 1000 copies/mL at 2 consecutive study visits at or after Study Week 96.

Reporting group title	PLB - ADV

Reporting group description:

Participants were randomized to receive placebo (PLB) to match ADV in the double-blind period (up to 48 weeks) followed by ADV in the open-label period (up to an additional 192 weeks). Lamivudine was added to the open-label ADV regimen of subjects between 12 and < 18 years old who had prior lamivudine exposure and who had a serum HBV DNA concentration ≥ 1000 copies/mL at 2 consecutive study visits at or after Study Week 96.

Primary: Percentage of Participants With Serum Hepatitis B Virus (HBV) Deoxyribonucleic Acid (DNA) < 1000 copies/mL (polymerase chain reaction [PCR]-based assay) and Normal Alanine Aminotransferase (ALT) at Week 48 (Missing = Failure)

End point title	Percentage of Participants With Serum Hepatitis B Virus (HBV) Deoxyribonucleic Acid (DNA) < 1000 copies/mL (polymerase chain reaction [PCR]-based assay) and Normal Alanine Aminotransferase (ALT) at Week 48 (Missing = Failure)

End point description:

In the absence of biopsy data from these pediatric participants, this endpoint enables assessments of drug effect on viral replication and the underlying degree of inflammation in the liver.

All randomized participants who received >= 1 dose study medication. If either endpoint was missing a Week 48 value, Week 44 value was substituted and used in the combined endpoint. If participant did not have serum HBV DNA value at Weeks 44 and 48 or ALT value at Weeks 44 and 48, then participant was considered a failure for the Week-48 analysis.

End point type	Primary

End point timeframe:

Week 48

End point values	ADV - ADV	PLB - ADV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	58		
Units: percentage of participants				
Baseline	0	0		
Week 24	5	0		
Week 48	19	2		

Statistical analyses

Statistical analysis title	P-value analysis

Statistical analysis description:

After unblinding the results, due to the small number of responders in the placebo group, it was determined that a statistical exact test would be more appropriate in the evaluation of treatment group differences than the originally planned 95% confidence intervals of the difference between the groups. Therefore, the results were analyzed by study visit, and a Fisher exact test was used to evaluate treatment differences between the adefovir dipivoxil and placebo groups.

Comparison groups	ADV - ADV v PLB - ADV
Number of subjects included in analysis	173
Analysis specification	Post-hoc
Analysis type	other[1]
P-value	< 0.001 [2]
Method	Fisher exact

Notes:

[1] - Intergroup comparison

[2] - End of double-blind treatment

Secondary: Percentage of Participants With Serum HBV DNA < 1000 Copies/mL (PCR-based Assay) While on Treatment (Missing = Failure) (ADV Baseline)

End point title	Percentage of Participants With Serum HBV DNA < 1000 Copies/mL (PCR-based Assay) While on Treatment (Missing = Failure) (ADV Baseline)

End point description:

The ADV baseline was defined as the day of first dose of ADV (ie, Week 0 for participants originally randomized to double-blind ADV [ADV-ADV group] and Week 48 for those originally randomized to placebo [PLB-ADV group]).

The open-label (OL) analysis set was used for this endpoint and included any participant who took at least 1 dose of open-label ADV. Participants with missing values were considered as failures rather than excluded.

End point type	Secondary

End point timeframe:

ADV baseline

End point values	ADV - ADV	PLB - ADV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	54		
Units: percentage of participants	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Serum HBV DNA < 1000 copies/mL (PCR-based assay) While on Treatment - Missing = Failure) (ADV Week 192)

End point title	Percentage of Participants With Serum HBV DNA < 1000 copies/mL (PCR-based assay) While on Treatment - Missing = Failure) (ADV Week 192)

End point description:

Adefovir week was defined as the windowed visit week relative to ADV baseline. Thus, participants in the

ADV-ADV group could have received up to 240 weeks of ADV treatment (ADV Week 240), whereas participants in the PLB-ADV group could receive only up to 192 weeks of ADV treatment (ADV Week 192).

The OL analysis set was used for this endpoint and included any participant who took at least 1 dose of open-label ADV. Participants with missing values were considered as failures rather than excluded.

End point type	Secondary

End point timeframe:

ADV Week 192

End point values	ADV - ADV	PLB - ADV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	54		
Units: percentage of participants	15	15		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary: Percentage of Participants With Serum HBV DNA < 1000 copies/mL (PCR-based assay) While on Treatment (Missing = Failure) (ADV Week 240)

End point title	Secondary: Percentage of Participants With Serum HBV DNA < 1000 copies/mL (PCR-based assay) While on Treatment (Missing = Failure) (ADV Week 240)[3]

End point description:

The OL analysis set was used for this endpoint and included any participant who took at least 1 dose of open-label ADV. Participants with missing values were considered as failures rather than excluded.

End point type	Secondary

End point timeframe:

ADV Week 240

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only participants randomized to the ADV-ADV arm completed 240 weeks of ADV treatment.

End point values	ADV - ADV			
Subject group type	Reporting group			
Number of subjects analysed	108			
Units: percentage of participants	6			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Serum HBV DNA < 400 copies/mL (PCR-

based assay) While on Treatment (Missing = Failure) (ADV Baseline)	
End point title	Percentage of Participants With Serum HBV DNA < 400 copies/mL (PCR-based assay) While on Treatment (Missing = Failure) (ADV Baseline)

End point description:

The ADV baseline was defined as the day of first dose of ADV (ie, Week 0 for participants originally randomized to double-blind ADV [ADV-ADV group] and Week 48 for those originally randomized to placebo [PLB-ADV group]).

The OL analysis set was used for this endpoint and included any participant who took at least 1 dose of open-label ADV. Participants with missing values were considered as failures rather than excluded.

End point type	Secondary

End point timeframe:

ADV baseline

End point values	ADV - ADV	PLB - ADV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	54		
Units: percentage of participants	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Serum HBV DNA < 400 copies/mL (PCR-based assay) While on Treatment (Missing = Failure) (ADV Week 192)	
End point title	Percentage of Participants With Serum HBV DNA < 400 copies/mL (PCR-based assay) While on Treatment (Missing = Failure) (ADV Week 192)

End point description:

Adefovir week was defined as the windowed visit week relative to ADV baseline. Thus, participants in the ADV-ADV group could have received up to 240 weeks of ADV treatment (ADV Week 240), whereas participants in the PLB-ADV group could receive only up to 192 weeks of ADV treatment (ADV Week 192).

The OL analysis set was used for this endpoint and included any participant who took at least 1 dose of open-label ADV. Participants with missing values were considered as failures rather than excluded.

End point type	Secondary

End point timeframe:

ADV Week 192

End point values	ADV - ADV	PLB - ADV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	54		
Units: percentage of participants	11	13		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Serum HBV DNA < 400 copies/mL (PCR-based assay) While on Treatment (Missing = Failure) (ADV Week 240)

End point title	Percentage of Participants With Serum HBV DNA < 400 copies/mL (PCR-based assay) While on Treatment (Missing = Failure) (ADV Week 240)[4]

End point description:

The OL analysis set was used for this endpoint and included any participant who took at least 1 dose of open-label ADV. Participants with missing values were considered as failures rather than excluded.

End point type	Secondary

End point timeframe:

ADV Week 240

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only participants randomized to the ADV-ADV arm completed 240 weeks of ADV treatment.

End point values	ADV - ADV			
Subject group type	Reporting group			
Number of subjects analysed	108			
Units: percentage of participants	6			

Statistical analyses

No statistical analyses for this end point

Secondary: ADV Baseline Serum HBV DNA

End point title	ADV Baseline Serum HBV DNA

End point description:

The ADV baseline was defined as the day of first dose of ADV (ie, Week 0 for participants originally randomized to double-blind ADV [ADV-ADV group] and Week 48 for those originally randomized to placebo [PLB-ADV group]).

The OL analysis set included any participant who took at least one dose of open-label ADV. This analysis set was also subdivided based on DB drug, as ADV-ADV or PLB-ADV. Analysis set included only data from participants while on study treatment.

End point type	Secondary

End point timeframe:

ADV baseline

End point values	ADV - ADV	PLB - ADV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	54		
Units: log10 HBV DNA copies/mL				
arithmetic mean (standard deviation)	8.76 (± 0.869)	8.24 (± 1.248)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from ADV Baseline to ADV Week 192 for Serum HBV DNA

End point title	Change from ADV Baseline to ADV Week 192 for Serum HBV DNA

End point description:

Adefovir week was defined as the windowed visit week relative to ADV baseline. Thus, participants in the ADV-ADV group could have received up to 240 weeks of ADV treatment (ADV Week 240), whereas participants in the PLB-ADV group could receive only up to 192 weeks of ADV treatment (ADV Week 192).

The OL analysis set included any participant who took at least one dose of open-label ADV. This analysis set was subdivided based on DB drug, as ADV-ADV or PLB-ADV. Analysis set included only data from participants while on study treatment.

End point type	Secondary

End point timeframe:

ADV baseline to ADV 192 weeks

End point values	ADV - ADV	PLB - ADV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	9		
Units: log10 HBV DNA copies/mL				
arithmetic mean (standard deviation)	-5.89 (± 1.119)	-5.41 (± 1.573)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from ADV Baseline to ADV Week 240 for Serum HBV DNA

End point title	Change from ADV Baseline to ADV Week 240 for Serum HBV DNA[5]

End point description:

The OL analysis set included any participant who took at least one dose of open-label ADV. This analysis

set was also subdivided based on DB drug, as ADV-ADV or PLB-ADV. Analysis set included only data from participants while on study treatment.

End point type	Secondary

End point timeframe:

ADV baseline to ADV 240 weeks

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only participants randomized to the ADV-ADV arm completed 240 weeks of ADV treatment.

End point values	ADV - ADV			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: log10 HBV DNA copies/mL				
arithmetic mean (standard deviation)	-5.87 (± 1.826)			

Statistical analyses

No statistical analyses for this end point

Secondary: ADV Baseline ALT

End point title	ADV Baseline ALT

End point description:

The ADV baseline was defined as the day of first dose of ADV (ie, Week 0 for participants originally randomized to double-blind ADV [ADV-ADV group] and Week 48 for those originally randomized to placebo [PLB-ADV group]).

The OL analysis set included any participant who took at least one dose of open-label ADV. This analysis set was also subdivided based on DB drug, as ADV-ADV or PLB-ADV. Analysis set included only data from participants while on study treatment.

End point type	Secondary

End point timeframe:

ADV baseline

End point values	ADV - ADV	PLB - ADV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	54		
Units: U/L				
arithmetic mean (standard deviation)	108.69 (± 79.069)	99.81 (± 97.583)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from ADV Baseline to ADV Week 192 for ALT

End point title	Change from ADV Baseline to ADV Week 192 for ALT

End point description:

Adefovir week was defined as the windowed visit week relative to ADV baseline. Thus, participants in the ADV-ADV group could have received up to 240 weeks of ADV treatment (ADV Week 240), whereas participants in the PLB-ADV group could receive only up to 192 weeks of ADV treatment (ADV Week 192).

The OL analysis set included any participant who took at least one dose of open-label ADV. This analysis set was subdivided based on DB drug, as ADV-ADV or PLB-ADV. Analysis set included only data from participants while on study
treatment.

End point type	Secondary

End point timeframe:

ADV baseline to ADV 192 weeks

End point values	ADV - ADV	PLB - ADV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	8		
Units: U/L				
arithmetic mean (standard deviation)	-66.06 (± 42.655)	-38.88 (± 33.566)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from ADV Baseline to ADV Week 240 for ALT

End point title	Change from ADV Baseline to ADV Week 240 for ALT[6]

End point description:

The OL analysis set included any participant who took at least one dose of open-label ADV. This analysis set was also subdivided based on DB drug, as ADV-ADV or PLB-ADV. Analysis set included only data from participants while on study treatment.

End point type	Secondary

End point timeframe:

ADV baseline to ADV 240 weeks

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only participants randomized to the ADV-ADV arm completed 240 weeks of ADV treatment.

End point values	ADV - ADV			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: U/L				
arithmetic mean (standard deviation)	-64.33 (± 44.742)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Normal ALT at Adefovir Baseline (Missing = Failure)

End point title	Percentage of Participants with Normal ALT at Adefovir Baseline (Missing = Failure)

End point description:

The ADV baseline was defined as the day of first dose of ADV (ie, Week 0 for participants originally randomized to double-blind ADV [ADV-ADV group] and Week 48 for those originally randomized to placebo [PLB-ADV group]). Normal ALT: 0-1 year old = <=54 U/L; females 1-88 years old and males 1-10 years old = 8-34 U/L; males 10-88 years old = 8-43 U/L.

The OL analysis set included any participant who took at least one dose of open-label ADV. This analysis set was also subdivided based on DB drug, as ADV-ADV or PLB-ADV. Participants with missing values were considered as failures rather than excluded. Analysis set included only data from participants while on study treatment.

End point type	Secondary

End point timeframe:

Adefovir baseline

End point values	ADV - ADV	PLB - ADV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	54		
Units: percentage of participants	7	15		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Normal ALT at ADV Week 192 (Missing = Failure)

End point title	Percentage of Participants with Normal ALT at ADV Week 192 (Missing = Failure)

End point description:

Adefovir week was defined as the windowed visit week relative to ADV baseline. Thus, participants in the ADV-ADV group could have received up to 240 weeks of ADV treatment (ADV Week 240), whereas participants in the PLB-ADV group could receive only up to 192 weeks of ADV treatment (ADV Week 192). Normal ALT: 0-1 year old = <=54 U/L; females 1-88 years old and males 1-10 years old = 8-34 U/L; males 10-88 years old = 8-43 U/L.

The OL analysis set included any participant who took at least one dose of open-label ADV. This analysis set was subdivided based on DB drug, as ADV-ADV or PLB-ADV. Participants with missing values were considered as failures rather than excluded. Analysis set included only data from participants while on

study
treatment.

End point type	Secondary

End point timeframe:

ADV Week 192

End point values	ADV - ADV	PLB - ADV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	54		
Units: percentage of participants	14	13		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Normal ALT at ADV Week 240 (Missing = Failure)

End point title	Percentage of Participants with Normal ALT at ADV Week 240 (Missing = Failure)[7]

End point description:

Normal ALT: 0-1 year old = <=54 U/L; females 1-88 years old and males 1-10 years old = 8-34 U/L; males 10-88 years old = 8-43 U/L.

The OL analysis set included any participant who took at least one dose of open-label ADV. This analysis set was subdivided based on DB drug, as ADV-ADV or PLB-ADV. Participants with missing values were considered as failures rather than excluded. Analysis set included only data from participants while on study treatment.

End point type	Secondary

End point timeframe:

ADV Week 240

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only participants randomized to the ADV-ADV arm completed 240 weeks of ADV treatment.

End point values	ADV - ADV			
Subject group type	Reporting group			
Number of subjects analysed	108			
Units: percentage of participants	5			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Hepatitis B e Antigen (HBeAg) Loss or Seroconversion by End of Blinded Treatment (Study Week 48; Randomized and

Treated Analysis Set)	
End point title	Percentage of Participants with Hepatitis B e Antigen (HBeAg) Loss or Seroconversion by End of Blinded Treatment (Study Week 48; Randomized and Treated Analysis Set)

End point description:

HBeAg loss is defined for an individual participant as HBeAg+ at ADV baseline and HBeAg− post baseline. HBeAg seroconversion is defined for an individual participant as HBeAg+ at ADV baseline and HBeAg− and hepatitis B e antibody + (anti-HBe+) post baseline.

The randomized and treated analysis set included all participants who were randomized into the study and received at least one dose of study medication. For Week 48 data; if Week 48 was missing, Week 44 was carried forward; if Week 44 was missing, missing = failure.

End point type	Secondary

End point timeframe:

Study Week 0 to Study Week 48 (double-blind period)

End point values	ADV - ADV	PLB - ADV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	57		
Units: percentage of participants				
HBeAg Loss	17	5		
Seroconversion to Anti-HBe	16	5		

Statistical analyses

Statistical analysis title	Comparison of HBeAg Loss
Comparison groups	ADV - ADV v PLB - ADV
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	other[8]
P-value	= 0.051 [9]
Method	Fisher exact

Notes:

[8] - Intergroup analysis

[9] - Comparison of HBeAg Loss

Statistical analysis title	Comparison of HBeAg Seroconversion
Comparison groups	ADV - ADV v PLB - ADV
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	other[10]
P-value	= 0.051 [11]
Method	Fisher exact

Notes:

[10] - Intergroup analysis

[11] - Comparison of HBeAg Seroconversion

Secondary: Percentage of Participants With HBeAg Loss or Seroconversion by ADV

Week 192 (Open Label Analysis Set, Participants Who Were HBeAg Positive at ADV Baseline; Missing = Excluded)

End point title	Percentage of Participants With HBeAg Loss or Seroconversion by ADV Week 192 (Open Label Analysis Set, Participants Who Were HBeAg Positive at ADV Baseline; Missing = Excluded)

End point description:

ADV baseline = 1st ADV-dose day = Week 0 for ADV-ADV group and Week 48 for PLB-ADV group. ADV week = windowed visit week relative to ADV baseline. Thus, participants in the ADV-ADV group could have received up to 240 weeks of ADV treatment (ADV Week 240), whereas participants in the PLB-ADV group could receive only up to 192 weeks of ADV treatment (ADV Week 192). HBeAg loss is defined per individual participant as HBeAg+ at ADV baseline and HBeAg− post baseline. HBeAg seroconversion is defined for an individual participant as HBeAg+ at ADV baseline and HBeAg− and anti-HBe+ post baseline.

The OL analysis set included any participant who took at least one dose of open-label ADV. This analysis set was subdivided based on DB drug, as ADV-ADV or PLB-ADV. Participants with missing values were excluded. Analysis set included only data from participants while on study treatment.

End point type	Secondary

End point timeframe:

ADV baseline to ADV Week 192

End point values	ADV - ADV	PLB - ADV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	9		
Units: percentage of participants				
HBeAg Loss	56	33		
Seroconversion to Anti-HBe	44	11		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With HBeAg Loss or Seroconversion by ADV Week 240 (Open Label Analysis Set, Participants Who Were HBeAg Positive at ADV Baseline; Missing = Excluded)

End point title	Percentage of Participants With HBeAg Loss or Seroconversion by ADV Week 240 (Open Label Analysis Set, Participants Who Were HBeAg Positive at ADV Baseline; Missing = Excluded)[12]

End point description:

Per protocol, participants could discontinue study medication due to HBeAg seroconversion and remain in the study in order to evaluate the durability of seroconversion. HBeAg loss is defined for an individual participant as HBeAg+ at ADV baseline and HBeAg− post baseline. HBeAg seroconversion is defined for an individual participant as HBeAg+ at ADV baseline and HBeAg− and anti-HBe+ post baseline.

The OL analysis set included any participant who took at least one dose of open-label ADV. This analysis set was subdivided based on DB drug, as ADV-ADV or PLB-ADV. Participants with missing values were excluded. Analysis set included only data from participants while on study treatment.

End point type	Secondary

End point timeframe:

ADV baseline to ADV Week 240

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only participants randomized to the ADV-ADV arm completed 240 weeks of ADV treatment.

End point values	ADV - ADV			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: percentage of participants				
HBeAg Loss	33			
Seroconversion to Anti-HBe	17			

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative Summary of Participants with HBV Genotypic Changes From Baseline (Resistance Surveillance)

End point title	Cumulative Summary of Participants with HBV Genotypic Changes From Baseline (Resistance Surveillance)

End point description:

Resistance surveillance was conducted annually for all participants who remained on treatment and had HBV DNA concentrations greater than or equal to the level of detection (>= 169 copies/mL) by PCR. The last on-ADV sample for all participants in the study was analyzed in the cumulative Week 240 resistance surveillance analysis.

Last on-ADV sample through Week 240 was analyzed, and participant was excluded from the cumulative Week 240 analysis if HBV DNA value was < 169 copies/mL at Week 240/last time point or if participant discontinued study drug but remained in study. One ADV-ADV participant had an ADV-specific, conserved-site mutation and is counted twice in the table.

End point type	Secondary

End point timeframe:

240 weeks

End point values	ADV - ADV	PLB - ADV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	37		
Units: participants				
No genotypic changes from baseline	48	18		
Polymorphic site changes	17	12		
Changes at conserved sites in HBV polymerase	3	3		
Developed mutations specific to ADV/lamivudine	1	0		
Unable to be genotyped	6	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative Summary of Participants with HBV Genotypic Changes From Baseline (Resistance Surveillance) for Subjects Who Received Combination ADV + Lamivudine Therapy

End point title	Cumulative Summary of Participants with HBV Genotypic Changes From Baseline (Resistance Surveillance) for Subjects Who Received Combination ADV + Lamivudine Therapy

End point description:

Resistance surveillance was conducted at Week 240/last on-treatment study visit for all participants who had HBV DNA concentrations greater than or equal to the level of detection (>= 169 copies/mL) by PCR while on combination ADV + lamivudine treatment. 32/173 added lamivudine from Weeks 108 - 144.

Last on-ADV sample through Week 240 analyzed; participant omitted from cumulative Week 240 analysis if HBV DNA <169 copies/mL at Week 240/last time point or stopped study drug but remained in study. 2 ADV-ADV participants had ADV/lamivudine-specific, conserved-site mutation, and counted 2x in table.

End point type	Secondary

End point timeframe:

240 weeks

End point values	ADV - ADV	PLB - ADV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	3		
Units: participants				
No genotypic changes from baseline	5	1		
Polymorphic site changes	3	1		
Changes at conserved sites in HBV polymerase	3	1		
Developed mutations specific to ADV and/or LAM	2	0		
Unable to be genotyped	3	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Durable HBeAg Seroconversion

End point title	Percentage of Participants with Durable HBeAg Seroconversion

End point description:

A participant was defined to have durable HBeAg seroconversion only if she/he remained in a seroconverted state (HBeAg−, hepatitis B e antibody + [anti-HBe+]) from the date that she/he first seroconverted through and including her/his last study visit. This endpoint could only be assessed for participants who (HBeAg−) seroconverted on-treatment and subsequently discontinued open-label dosing.

Participants who discontinued treatment because of confirmed HBeAg seroconversion in Weeks 49 to 240 were to remain in the study through Week 240 to monitor the durability of seroconversion. Any participant who formally stopped drug early and restarted, by definition, did not have durable HBeAg seroconversion.

End point type	Secondary

End point timeframe:

240 weeks

End point values	ADV - ADV	PLB - ADV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	24		
Units: percentage of participants	82	71		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 240 weeks (during the 48 weeks of randomized treatment and subsequent 192 weeks of open-label treatment) plus 30 days.

Adverse event reporting additional description:

Double-blind phase: up to 48 weeks (plus 4 days for participants who discontinued early, or plus 30 days if participants completed the double-blind phase but did not enter the open label phase). Open-label phase: from Week 48 up to Week 240 plus 30 days.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.0

Reporting groups

Reporting group title	ADV (Double-Blind)

Reporting group description:

Adverse events in this reporting group include those occurring in participants who received ADV in the doubleblind
phase.

Reporting group title	PLB (Double-Blind)

Reporting group description:

Adverse events in this reporting group include those occurring in participants who received placebo to match ADV in the double-blind phase.

Reporting group title	ADV-ADV (open-label, on treatment)

Reporting group description:

Adverse events in this reporting group include those occurring while on treatment in the open-label phase in participants originally randomized to ADV in the double-blind phase, and who then continued ADV treatment in the open-label phase.

Reporting group title	PLB-ADV (open-label, on treatment)

Reporting group description:

Adverse events in this reporting group include those occurring while on treatment in the open-label phase in participants originally randomized to placebo to match ADV in the double-blind phase, and who then switched to ADV treatment in the open-label phase.

Reporting group title	ADV-ADV (open-label, off treatment)

Reporting group description:

Adverse events in this reporting group include those occurring while off treatment in the open-label phase in participants originally randomized to ADV in the double-blind phase, and who then continued ADV treatment in the open-label phase.

Reporting group title	PLB-ADV (open-label, off treatment)

Reporting group description:

Adverse events in this reporting group include those occurring while off treatment in the open-label phase in participants originally randomized to placebo to match ADV in the double-blind phase, and who then switched to ADV treatment in the open-label phase.

Serious adverse events	ADV (Double-Blind)	PLB (Double-Blind)	ADV-ADV (open-label, on treatment)
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 115 (6.09%)	5 / 58 (8.62%)	10 / 108 (9.26%)
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	0 / 115 (0.00%)	1 / 58 (1.72%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 115 (0.00%)	0 / 58 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme increased			
subjects affected / exposed	1 / 115 (0.87%)	0 / 58 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			
subjects affected / exposed	0 / 115 (0.00%)	0 / 58 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	0 / 115 (0.00%)	0 / 58 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint injury			
subjects affected / exposed	0 / 115 (0.00%)	0 / 58 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Excoriation			
subjects affected / exposed	0 / 115 (0.00%)	0 / 58 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extradural haematoma			

subjects affected / exposed	0 / 115 (0.00%)	0 / 58 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial bones fracture			
subjects affected / exposed	0 / 115 (0.00%)	0 / 58 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Forearm fracture			
subjects affected / exposed	0 / 115 (0.00%)	0 / 58 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture			
subjects affected / exposed	1 / 115 (0.87%)	0 / 58 (0.00%)	0 / 108 (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
Hand fracture			
subjects affected / exposed	0 / 115 (0.00%)	0 / 58 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	1 / 115 (0.87%)	0 / 58 (0.00%)	0 / 108 (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
Injury			
subjects affected / exposed	0 / 115 (0.00%)	0 / 58 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaw fracture			
subjects affected / exposed	0 / 115 (0.00%)	0 / 58 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint dislocation			

subjects affected / exposed	0 / 115 (0.00%)	0 / 58 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			
subjects affected / exposed	0 / 115 (0.00%)	0 / 58 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 115 (0.00%)	0 / 58 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound			
subjects affected / exposed	0 / 115 (0.00%)	0 / 58 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 115 (0.00%)	0 / 58 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope vasovagal			
subjects affected / exposed	1 / 115 (0.87%)	0 / 58 (0.00%)	0 / 108 (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
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 115 (1.74%)	0 / 58 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 115 (0.00%)	0 / 58 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Abdominal pain upper			
subjects affected / exposed	0 / 115 (0.00%)	0 / 58 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 115 (0.87%)	0 / 58 (0.00%)	0 / 108 (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
Dyspepsia			
subjects affected / exposed	0 / 115 (0.00%)	1 / 58 (1.72%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	1 / 115 (0.87%)	0 / 58 (0.00%)	0 / 108 (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
Reproductive system and breast disorders			
Testicular haemorrhage			
subjects affected / exposed	0 / 115 (0.00%)	0 / 58 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	0 / 115 (0.00%)	1 / 58 (1.72%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	0 / 115 (0.00%)	0 / 58 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			

subjects affected / exposed	0 / 115 (0.00%)	0 / 58 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abnormal behaviour			
subjects affected / exposed	1 / 115 (0.87%)	0 / 58 (0.00%)	0 / 108 (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
Mental disorder			
subjects affected / exposed	0 / 115 (0.00%)	0 / 58 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Osteochondrosis			
subjects affected / exposed	0 / 115 (0.00%)	0 / 58 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Gastroenteritis bacterial			
subjects affected / exposed	0 / 115 (0.00%)	1 / 58 (1.72%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis B			
subjects affected / exposed	0 / 115 (0.00%)	0 / 58 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lyme disease			
subjects affected / exposed	0 / 115 (0.00%)	0 / 58 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral herpes			
subjects affected / exposed	0 / 115 (0.00%)	0 / 58 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pneumonia			
subjects affected / exposed	0 / 115 (0.00%)	1 / 58 (1.72%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Typhus			
subjects affected / exposed	0 / 115 (0.00%)	0 / 58 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	PLB-ADV (open-label, on treatment)	ADV-ADV (open-label, off treatment)	PLB-ADV (open-label, off treatment)
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 54 (5.56%)	30 / 108 (27.78%)	10 / 54 (18.52%)
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 / 54 (1.85%)	6 / 108 (5.56%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	1 / 1	4 / 6	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 54 (0.00%)	2 / 108 (1.85%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme increased			
subjects affected / exposed	0 / 54 (0.00%)	0 / 108 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			
subjects affected / exposed	0 / 54 (0.00%)	1 / 108 (0.93%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Alcohol poisoning			

subjects affected / exposed	1 / 54 (1.85%)	0 / 108 (0.00%)	0 / 54 (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
Joint injury			
subjects affected / exposed	1 / 54 (1.85%)	0 / 108 (0.00%)	0 / 54 (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
Excoriation			
subjects affected / exposed	0 / 54 (0.00%)	0 / 108 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extradural haematoma			
subjects affected / exposed	0 / 54 (0.00%)	1 / 108 (0.93%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial bones fracture			
subjects affected / exposed	0 / 54 (0.00%)	0 / 108 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Forearm fracture			
subjects affected / exposed	0 / 54 (0.00%)	1 / 108 (0.93%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture			
subjects affected / exposed	0 / 54 (0.00%)	0 / 108 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hand fracture			
subjects affected / exposed	0 / 54 (0.00%)	0 / 108 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			

subjects affected / exposed	0 / 54 (0.00%)	0 / 108 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury			
subjects affected / exposed	0 / 54 (0.00%)	1 / 108 (0.93%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaw fracture			
subjects affected / exposed	0 / 54 (0.00%)	1 / 108 (0.93%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint dislocation			
subjects affected / exposed	0 / 54 (0.00%)	0 / 108 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			
subjects affected / exposed	0 / 54 (0.00%)	0 / 108 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 54 (0.00%)	0 / 108 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound			
subjects affected / exposed	0 / 54 (0.00%)	0 / 108 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 54 (0.00%)	1 / 108 (0.93%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope vasovagal			

subjects affected / exposed	0 / 54 (0.00%)	0 / 108 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 54 (0.00%)	0 / 108 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 54 (0.00%)	0 / 108 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 54 (0.00%)	0 / 108 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 54 (0.00%)	0 / 108 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspepsia			
subjects affected / exposed	0 / 54 (0.00%)	0 / 108 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 54 (0.00%)	0 / 108 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Testicular haemorrhage			

subjects affected / exposed	0 / 54 (0.00%)	1 / 108 (0.93%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	0 / 54 (0.00%)	19 / 108 (17.59%)	5 / 54 (9.26%)
occurrences causally related to treatment / all	0 / 0	11 / 19	2 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	0 / 54 (0.00%)	0 / 108 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 54 (1.85%)	0 / 108 (0.00%)	0 / 54 (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
Abnormal behaviour			
subjects affected / exposed	0 / 54 (0.00%)	0 / 108 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental disorder			
subjects affected / exposed	0 / 54 (0.00%)	0 / 108 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Osteochondrosis			
subjects affected / exposed	0 / 54 (0.00%)	0 / 108 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Gastroenteritis bacterial			

subjects affected / exposed	0 / 54 (0.00%)	0 / 108 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis B			
subjects affected / exposed	0 / 54 (0.00%)	1 / 108 (0.93%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lyme disease			
subjects affected / exposed	0 / 54 (0.00%)	1 / 108 (0.93%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral herpes			
subjects affected / exposed	0 / 54 (0.00%)	0 / 108 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 54 (0.00%)	0 / 108 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Typhus			
subjects affected / exposed	0 / 54 (0.00%)	1 / 108 (0.93%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	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	ADV (Double-Blind)	PLB (Double-Blind)	ADV-ADV (open-label, on treatment)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	77 / 115 (66.96%)	41 / 58 (70.69%)	58 / 108 (53.70%)
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	2 / 115 (1.74%)	1 / 58 (1.72%)	0 / 108 (0.00%)
occurrences (all)	2	1	0
Nervous system disorders			

Headache			
subjects affected / exposed	15 / 115 (13.04%)	8 / 58 (13.79%)	11 / 108 (10.19%)
occurrences (all)	24	12	14
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	14 / 115 (12.17%)	5 / 58 (8.62%)	5 / 108 (4.63%)
occurrences (all)	22	9	5
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	10 / 115 (8.70%)	9 / 58 (15.52%)	9 / 108 (8.33%)
occurrences (all)	12	19	10
Diarrhoea			
subjects affected / exposed	7 / 115 (6.09%)	4 / 58 (6.90%)	5 / 108 (4.63%)
occurrences (all)	10	5	5
Vomiting			
subjects affected / exposed	4 / 115 (3.48%)	5 / 58 (8.62%)	4 / 108 (3.70%)
occurrences (all)	4	7	4
Abdominal pain upper			
subjects affected / exposed	4 / 115 (3.48%)	1 / 58 (1.72%)	4 / 108 (3.70%)
occurrences (all)	4	1	7
Toothache			
subjects affected / exposed	1 / 115 (0.87%)	3 / 58 (5.17%)	5 / 108 (4.63%)
occurrences (all)	1	5	5
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	17 / 115 (14.78%)	12 / 58 (20.69%)	6 / 108 (5.56%)
occurrences (all)	25	17	7
Pharyngolaryngeal pain			
subjects affected / exposed	7 / 115 (6.09%)	4 / 58 (6.90%)	3 / 108 (2.78%)
occurrences (all)	7	5	6
Epistaxis			
subjects affected / exposed	2 / 115 (1.74%)	5 / 58 (8.62%)	6 / 108 (5.56%)
occurrences (all)	2	7	8
Skin and subcutaneous tissue disorders			
Rash			

subjects affected / exposed	3 / 115 (2.61%)	3 / 58 (5.17%)	7 / 108 (6.48%)
occurrences (all)	3	3	8
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	30 / 115 (26.09%)	14 / 58 (24.14%)	12 / 108 (11.11%)
occurrences (all)	37	15	15
Pharyngitis			
subjects affected / exposed	15 / 115 (13.04%)	7 / 58 (12.07%)	14 / 108 (12.96%)
occurrences (all)	21	7	21
Upper respiratory tract infection			
subjects affected / exposed	13 / 115 (11.30%)	8 / 58 (13.79%)	6 / 108 (5.56%)
occurrences (all)	21	12	9
Bronchitis			
subjects affected / exposed	8 / 115 (6.96%)	4 / 58 (6.90%)	6 / 108 (5.56%)
occurrences (all)	8	5	6
Tonsillitis			
subjects affected / exposed	2 / 115 (1.74%)	2 / 58 (3.45%)	4 / 108 (3.70%)
occurrences (all)	2	2	4
Rhinitis			
subjects affected / exposed	5 / 115 (4.35%)	9 / 58 (15.52%)	2 / 108 (1.85%)
occurrences (all)	7	12	4
Influenza			
subjects affected / exposed	4 / 115 (3.48%)	3 / 58 (5.17%)	2 / 108 (1.85%)
occurrences (all)	6	3	2
Gastroenteritis			
subjects affected / exposed	1 / 115 (0.87%)	3 / 58 (5.17%)	2 / 108 (1.85%)
occurrences (all)	1	4	2
Otitis media			
subjects affected / exposed	2 / 115 (1.74%)	2 / 58 (3.45%)	0 / 108 (0.00%)
occurrences (all)	3	2	0

Non-serious adverse events	PLB-ADV (open-label, on treatment)	ADV-ADV (open-label, off treatment)	PLB-ADV (open-label, off treatment)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 54 (70.37%)	33 / 108 (30.56%)	19 / 54 (35.19%)
Investigations			

Blood creatine phosphokinase increased			
subjects affected / exposed	5 / 54 (9.26%)	0 / 108 (0.00%)	0 / 54 (0.00%)
occurrences (all)	5	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 54 (7.41%)	4 / 108 (3.70%)	2 / 54 (3.70%)
occurrences (all)	8	4	3
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	3 / 54 (5.56%)	6 / 108 (5.56%)	7 / 54 (12.96%)
occurrences (all)	5	8	8
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	10 / 54 (18.52%)	4 / 108 (3.70%)	2 / 54 (3.70%)
occurrences (all)	13	4	2
Diarrhoea			
subjects affected / exposed	3 / 54 (5.56%)	4 / 108 (3.70%)	3 / 54 (5.56%)
occurrences (all)	5	4	6
Vomiting			
subjects affected / exposed	2 / 54 (3.70%)	2 / 108 (1.85%)	3 / 54 (5.56%)
occurrences (all)	2	2	3
Abdominal pain upper			
subjects affected / exposed	3 / 54 (5.56%)	0 / 108 (0.00%)	1 / 54 (1.85%)
occurrences (all)	5	0	1
Toothache			
subjects affected / exposed	1 / 54 (1.85%)	2 / 108 (1.85%)	0 / 54 (0.00%)
occurrences (all)	1	2	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 54 (1.85%)	4 / 108 (3.70%)	1 / 54 (1.85%)
occurrences (all)	1	5	1
Pharyngolaryngeal pain			
subjects affected / exposed	1 / 54 (1.85%)	2 / 108 (1.85%)	0 / 54 (0.00%)
occurrences (all)	1	3	0
Epistaxis			

subjects affected / exposed	1 / 54 (1.85%)	2 / 108 (1.85%)	0 / 54 (0.00%)
occurrences (all)	2	2	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	3 / 54 (5.56%)	3 / 108 (2.78%)	1 / 54 (1.85%)
occurrences (all)	7	4	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	8 / 54 (14.81%)	3 / 108 (2.78%)	7 / 54 (12.96%)
occurrences (all)	9	3	11
Pharyngitis			
subjects affected / exposed	12 / 54 (22.22%)	8 / 108 (7.41%)	6 / 54 (11.11%)
occurrences (all)	20	12	8
Upper respiratory tract infection			
subjects affected / exposed	4 / 54 (7.41%)	4 / 108 (3.70%)	1 / 54 (1.85%)
occurrences (all)	6	9	2
Bronchitis			
subjects affected / exposed	4 / 54 (7.41%)	2 / 108 (1.85%)	2 / 54 (3.70%)
occurrences (all)	4	2	2
Tonsillitis			
subjects affected / exposed	5 / 54 (9.26%)	1 / 108 (0.93%)	4 / 54 (7.41%)
occurrences (all)	8	1	4
Rhinitis			
subjects affected / exposed	1 / 54 (1.85%)	0 / 108 (0.00%)	0 / 54 (0.00%)
occurrences (all)	1	0	0
Influenza			
subjects affected / exposed	3 / 54 (5.56%)	2 / 108 (1.85%)	0 / 54 (0.00%)
occurrences (all)	3	3	0
Gastroenteritis			
subjects affected / exposed	1 / 54 (1.85%)	2 / 108 (1.85%)	0 / 54 (0.00%)
occurrences (all)	1	2	0
Otitis media			
subjects affected / exposed	3 / 54 (5.56%)	1 / 108 (0.93%)	0 / 54 (0.00%)
occurrences (all)	3	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 August 2004	The estimated number of subjects to be enrolled was changed from 135 to 150 subjects to provide an adequate safety database.
07 July 2006	Changed the management of subjects with a serum HBV DNA concentration ≥ 1000 copies/mL at 2 consecutive study visits at or after Week 96. The amendment required that lamivudine (LAM) be added to the ADV regimen for such subjects.
06 February 2007	Provided recommended treatment options based upon HBV DNA levels and/or age and prior lamivudine exposure in order to reduce risk of developing resistance.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

There were no limitations affecting the analysis or results.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/18433023