Clinical trial results:
Phase III study of adefovir dipivoxil in patients with treatment naïve CHB. Comparator is Lamivudine 100mcg film coated tablets-D2012-7213

Summary

EudraCT number	2015-004890-34
Trial protocol	Outside EU/EEA
Global end of trial date	16 January 2008

Results information

Result version number	v1 (current)
This version publication date	22 January 2017
First version publication date	22 January 2017

Trial information

Trial identification

Sponsor protocol code	ADF105220

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom,
Public contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,

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	17 March 2008
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 January 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

TBD

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 January 2006
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Japan: 105
Worldwide total number of subjects	105
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	105
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

In this study, informed consent was obtained from 171 subjects. Of those subjects, 66 were withdrawn for not meeting eligibility criteria at screening, including 2 for consent withdrawn.

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	Investigator, Subject, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Adefovir (ADV)

Arm description:

ADV 10 mg orally once daily for 52 weeks

Arm type	Experimental
Investigational medicinal product name	Adefovir dipivoxil (ADV)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects were administered one ADV 10 mg tablet and one LAM placebo tablet orally once daily for 52 weeks

Arm title	Lamivudine (LAM)

Arm description:

LAM 100 mg orally once daily for 52 weeks

Arm type	Active comparator
Investigational medicinal product name	Lamivudine (LAM)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects were administered one LAM 100 mg tablet and one ADV placebo tablet orally once daily for 52 weeks

Number of subjects in period 1	Adefovir (ADV)	Lamivudine (LAM)
Started	52	53
Completed	50	47
Not completed	2	6
Adverse event, non-fatal	-	6
Consent withdrawn	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Adefovir (ADV)
Reporting group description: ADV 10 mg orally once daily for 52 weeks	
Reporting group title	Lamivudine (LAM)
Reporting group description: LAM 100 mg orally once daily for 52 weeks	

Reporting group values	Adefovir (ADV)	Lamivudine (LAM)	Total
Number of subjects	52	53	105
Age categorical Units: Subjects			
Age continuous			
Age continuous description			
Units: years			
arithmetic mean	44	43.9	
standard deviation	± 9.73	± 9.95	-
Gender categorical			
Gender categorical description			
Units: Subjects			
Female	9	18	27
Male	43	35	78
Race/Ethnicity, Customized Units: Subjects			
Asian	52	53	105
Region of Enrollment Units: Subjects			
Japan	52	53	105

End points

End points reporting groups	
Reporting group title	Adefovir (ADV)
Reporting group description: ADV 10 mg orally once daily for 52 weeks	
Reporting group title	Lamivudine (LAM)
Reporting group description: LAM 100 mg orally once daily for 52 weeks	

Primary: Mean Change from Baseline in Hepatitis B Virus (HBV) DNA at Week 52	
End point title	Mean Change from Baseline in Hepatitis B Virus (HBV) DNA at Week 52
End point description: Change from baseline was the difference of the HBV DNA copy numbers (log10) in serum collected by blood draw between baseline and Week 52. Per Protocol Set (PPS): participants in the Full Analysis Set (all subjects who entered the study, received at least one dose of investigational product, and had at least one efficacy assessment after the treatment initiation) population with no major protocol violations.	
End point type	Primary
End point timeframe: Baseline and Week 52	

End point values	Adefovir (ADV)	Lamivudine (LAM)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50[1]	52[2]		
Units: log10 copies/mL				
arithmetic mean (standard deviation)	-3.69 (± 1.169)	-3.4 (± 1.896)		

Notes:

[1] - PPS

[2] - PPS

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Lamivudine (LAM) v Adefovir (ADV)
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Median difference (net)
Point estimate	-0.33

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.94
upper limit	0.28
Variability estimate	Standard error of the mean
Dispersion value	0.309

Notes:

[3] - This is a Non-inferiority Analysis with the margin of -1.0.

Secondary: Percentage of participants with HBV DNA Loss (<400 copies/mL) at Week 52

End point title	Percentage of participants with HBV DNA Loss (<400 copies/mL) at Week 52

End point description:

The percentages of participants with an HBV DNA level in serum of less than 400 copies/mL, which is the lower limit of detection (HBV DNA loss) at Week 52

End point type	Secondary

End point timeframe:

Week 52

End point values	Adefovir (ADV)	Lamivudine (LAM)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50[4]	52[5]		
Units: Percentage of participants				
number (not applicable)				
<400 copies/mL	46	50		
>400 copies/mL	54	50		

Notes:

[4] - PPS

[5] - PPS

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with Hepatitis B e antigen (HBeAg) loss at Week 52

End point title	Percentage of participants with Hepatitis B e antigen (HBeAg) loss at Week 52

End point description:

Participants with loss of Hepatitis B e antigen (HBeAg) in serum collected by blood draw: Cheminoluminescent Immuno Assay (CLIA) method

End point type	Secondary

End point timeframe:

Week 52

End point values	Adefovir (ADV)	Lamivudine (LAM)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36[6]	37[7]		
Units: percentage of participants				
number (not applicable)				
With loss of HBeAg	16.7	16.2		
Positive for HBeAg	93.3	93.8		

Notes:

[6] - PPS

[7] - PPS

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with Hepatitis B e antigen/antibody (HBeAg/Ab) Seroconversion at Week 52

End point title	Percentage of participants with Hepatitis B e antigen/antibody (HBeAg/Ab) Seroconversion at Week 52

End point description:

Participants with loss of Hepatitis B e antigen (HBeAg) and positive for anti-Hepatitis B e antibody (HBeAb) in serum collected by blood draw: CLIA method

End point type	Secondary

End point timeframe:

Week 52

End point values	Adefovir (ADV)	Lamivudine (LAM)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31[8]	34[9]		
Units: Percentage of participants				
number (not applicable)				
With HBeAg/Ab seroconversion	9.7	5.9		
Without HBeAg/Ab seroconversion	90.3	94.1		

Notes:

[8] - PPS: participants who were positive for HBeAg and negative for HBeAb at baseline

[9] - PPS: participants who were positive for HBeAg and negative for HBeAb at baseline

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with Hepatitis B s antigen (HBsAg) loss at Week 52

End point title	Percentage of participants with Hepatitis B s antigen (HBsAg) loss at Week 52

End point description:

Participants with loss of Hepatitis B s antigen (HBsAg) in serum collected by blood draw: CLIA method

End point type	Secondary

End point timeframe:

Week 52

End point values	Adefovir (ADV)	Lamivudine (LAM)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50[10]	52[11]		
Units: percentage of participants				
number (not applicable)				
With loss of HBsAg	0	0		
Positive for HBsAg	100	100		

Notes:

[10] - PPS: participants who were positive for HBeAg at baseline

[11] - PPS: participants who were positive for HBeAg at baseline

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with Hepatitis B s antigen/ antibody (HBsAg/Ab) Seroconversion at Week 52

End point title	Percentage of participants with Hepatitis B s antigen/ antibody (HBsAg/Ab) Seroconversion at Week 52

End point description:

Participants with loss of Hepatitis B s antigen (HBsAg) and positive for anti-Hepatitis B s antibody (HBsAb) in serum collected by blood draw: CLIA method

End point type	Secondary

End point timeframe:

Week 52

End point values	Adefovir (ADV)	Lamivudine (LAM)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46[12]	45[13]		
Units: percentage of participants				
number (not applicable)				
With HBsAg/Ab seroconversion	0	0		
Without HBsAg/Ab seroconversion	100	100		

Notes:

[12] - PPS: participants who were positive for HBeAg and negative for HBeAb at baseline

[13] - PPS: participants who were positive for HBeAg and negative for HBeAb at baseline

Statistical analyses

No statistical analyses for this end point

Secondary: Mean alanine aminotransferase (ALT) level at Week 52

End point title	Mean alanine aminotransferase (ALT) level at Week 52

End point description:

Summary statistics were displayed for serum ALT.

End point type	Secondary

End point timeframe:

Week 52

End point values	Adefovir (ADV)	Lamivudine (LAM)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50[14]	47[15]		
Units: Units per Liter				
arithmetic mean (standard deviation)	32.3 (± 14.72)	33 (± 28.12)		

Notes:

[14] - PPS

[15] - PPS

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with alanine aminotransferase (ALT) normalization at Week 52

End point title	Percentage of participants with alanine aminotransferase (ALT) normalization at Week 52

End point description:

ALT normalization was defined as an ALT value that was in the normal range (<= 45IU/L; upper limit of normal [ULN]) at Week 52 of the participants whose ALT values were abnormal (>45IU/L) at baseline

End point type	Secondary

End point timeframe:

Week 52

End point values	Adefovir (ADV)	Lamivudine (LAM)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46[16]	51[17]		
Units: Percentage of participants				
number (not applicable)				
With ALT normalization	82.6	78.4		
Without ALT normalization	17.4	21.6		

Notes:

[16] - PPS: Participants with abnormal ALT value (>ULN) at baseline

[17] - PPS: Participants with abnormal ALT value (>ULN) at baseline

Statistical analyses

No statistical analyses for this end point

Secondary: Time to onset of ALT normalization

End point title	Time to onset of ALT normalization

End point description:

Time to onset of ALT normalization was summarized using the Kaplan-Meier method.

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Adefovir (ADV)	Lamivudine (LAM)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46[18]	51[19]		
Units: Week 52				
median (confidence interval 95%)	12 (8 to 16)	12 (12 to 16)		

Notes:

[18] - PPS: Participants with abnormal ALT value (>ULN) at baseline

[19] - PPS: Participants with abnormal ALT value (>ULN) at baseline

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Emergence of Resistant Virus at Week 52

End point title	Rate of Emergence of Resistant Virus at Week 52

End point description:

Participants with resistant mutation at Week 52. LAM resistant mutation (enzyme-linked mini-sequencing assay): rtM204I/V; ADV resistant mutation (direct sequencing assay): rtN236T or rtA181T/V in HBV DNA ; rt: reverse transcriptase gene

End point type	Secondary

End point timeframe:

Week 52

End point values	Adefovir (ADV)	Lamivudine (LAM)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50[20]	52[21]		
Units: Percentage of participants				
number (not applicable)				
With resistant mutation	0	28.8		
Without resistant mutation	100	71.2		

Notes:

[20] - PPS

[21] - PPS

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From Baseline to Week 52.	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	9.0
Reporting groups	
Reporting group title	Adefovir (ADV)
Reporting group description: ADV 10 mg orally once daily for 52 weeks	
Reporting group title	Lamivudine (LAM)
Reporting group description: LAM 100 mg orally once daily for 52 weeks	

Serious adverse events	Adefovir (ADV)	Lamivudine (LAM)	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 52 (0.00%)	4 / 53 (7.55%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lymphoma			
alternative dictionary used: MedDRA 9.0			
subjects affected / exposed	0 / 52 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatitis			
alternative dictionary used: MedDRA 9.0			
subjects affected / exposed	0 / 52 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary retention			
alternative dictionary used: MedDRA 9.0			

subjects affected / exposed	0 / 52 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia bacterial			
alternative dictionary used: MedDRA 9.0			
subjects affected / exposed	0 / 52 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Adefovir (ADV)	Lamivudine (LAM)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 52 (75.00%)	47 / 53 (88.68%)	
Investigations			
Blood creatine phosphokinase increased			
alternative dictionary used: MedDRA 9.0			
subjects affected / exposed	5 / 52 (9.62%)	4 / 53 (7.55%)	
occurrences (all)	8	5	
Nervous system disorders			
Headache			
alternative dictionary used: MedDRA 9.0			
subjects affected / exposed	1 / 52 (1.92%)	4 / 53 (7.55%)	
occurrences (all)	1	9	
General disorders and administration site conditions			
Malaise			
alternative dictionary used: MedDRA 9.0			
subjects affected / exposed	2 / 52 (3.85%)	5 / 53 (9.43%)	
occurrences (all)	3	5	
Gastrointestinal disorders			
Diarrhea			
alternative dictionary used: MedDRA 9.0			
subjects affected / exposed	7 / 52 (13.46%)	6 / 53 (11.32%)	
occurrences (all)	10	6	

Abdominal pain upper alternative dictionary used: MedDRA 9.0 subjects affected / exposed occurrences (all) Nausea alternative dictionary used: MedDRA 9.0 subjects affected / exposed occurrences (all) Vomiting alternative dictionary used: MedDRA 9.0 subjects affected / exposed occurrences (all)	3 / 52 (5.77%) 3 1 / 52 (1.92%) 1 0 / 52 (0.00%) 1	2 / 53 (3.77%) 2 4 / 53 (7.55%) 4 3 / 53 (5.66%) 4	
Respiratory, thoracic and mediastinal disorders Pharyngolaryngeal pain alternative dictionary used: MedDRA 9.0 subjects affected / exposed occurrences (all) Cough alternative dictionary used: MedDRA 9.0 subjects affected / exposed occurrences (all)	2 / 52 (3.85%) 2 2 / 52 (3.85%) 2	5 / 53 (9.43%) 5 3 / 53 (5.66%) 3	
Hepatobiliary disorders Hepatitis alternative dictionary used: MedDRA 9.0 subjects affected / exposed occurrences (all)	0 / 52 (0.00%) 0	6 / 53 (11.32%) 6	
Skin and subcutaneous tissue disorders Eczema alternative dictionary used: MedDRA 9.0 subjects affected / exposed occurrences (all)	5 / 52 (9.62%) 5	3 / 53 (5.66%) 4	
Musculoskeletal and connective tissue disorders Arthralgia alternative dictionary used: MedDRA 9.0			

subjects affected / exposed	3 / 52 (5.77%)	0 / 53 (0.00%)	
occurrences (all)	3	0	
Infections and infestations			
Nasopharyngitis			
alternative dictionary used: MedDRA 9.0			
subjects affected / exposed	11 / 52 (21.15%)	19 / 53 (35.85%)	
occurrences (all)	15	27	
Upper respiratory tract inflammation			
alternative dictionary used: MedDRA 9.0			
subjects affected / exposed	7 / 52 (13.46%)	10 / 53 (18.87%)	
occurrences (all)	11	11	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 February 2006	Revised the description of contraindication medications in the exclusion criteria: transferred the statement "(except ointment and/or cream etc)" to the first sentence, because this statement relates to not only corticosteroid but also entire contraindication medications.
17 March 2006	Changed the commencement of the period of contraindication medications from the first day of the screening period to the first dosing day.
19 September 2006	Modified the study administrative structure
16 April 2007	Modified the study administrative structure

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported