Clinical trial results:
MK-0518B (EU Sourced Lamivudine) Bioequivalence Study
Summary

EudraCT number	2014-004767-21
Trial protocol	Outside EU/EEA
Global end of trial date	22 October 2012

Results information

Result version number	v1
This version publication date	05 April 2016
First version publication date	19 July 2015

Trial information

Trial identification

Sponsor protocol code	MK-0518B-258

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001442-PIP01-13
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	22 October 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 October 2012
Global end of trial reached?	Yes
Global end of trial date	22 October 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study aimed to evaluate the comparative bioavailability between Raltegravir/Lamivudine (MK-0518B) 300 mg/150 mg fixed dose combination (FDC) tablets, with a 400 mg Raltegravir tablet co-administered with a 150 mg Lamivudine tablet, after a single-dose administration in healthy participants under fasting conditions. The primary hypotheses were as follows: for Raltegravir the 90% confidence intervals of the geometric mean ratio (GMR, FDC/separate tablets) of area under the concentration curve from time 0 to the time of last measurable analyte (AUC0-t) should be between 80.00 and 125.00%; for Raltegravir the 90% confidence intervals of the geometric mean ratio (GMR, FDC/separate tablets) of the plasma concentration at 12 hours post administration (C12hr) should be between 80.00 and 200.00%; and for Lamivudine the 90% confidence intervals of the geometric mean ratio (GMR, FDC/separate tablets) of AUC0-t and the maximum plasma concentration (Cmax) should be between 80.00 and 125.00%.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 October 2012
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	Canada: 108
Worldwide total number of subjects	108
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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	108
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Healthy, non-smoking, male and female volunteers from 18 to 55 years of age, with a Body Mass Index (BMI) ≥18.5 and ≤ 30.0 kg/m^2 were enrolled in this study.

Period 1

Period 1 title	Crossover Period 1
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Arm title	All treated participants

Arm description:

Participants were assigned to one of the following two crossover treatment sequences: one FDC tablet containing both Raltegravir and Lamivudine in Period 1; followed by individual Raltegravir and Lamivudine tablets in Period 2; or vice versa. Period 1 was separated from Period 2 by a minimum of 7 days washout. The population analysed was all participants who received at least one administration of study treatment.

Arm type	Experimental
Investigational medicinal product name	Raltegravir/lamivudine 300 mg/150 mg FDC tablets
Investigational medicinal product code	
Other name	MK-0518B
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

A single Raltegravir/lamivudine 300 mg/150 mg FDC tablet was administered orally, under fasting conditions at the start of each crossover period.

Investigational medicinal product name	Raltegravir
Investigational medicinal product code	
Other name	Isentress
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

A single Raltegravir 400 mg tablet was administered orally, under fasting conditions at the start of each crossover period.

Investigational medicinal product name	Lamivudine
Investigational medicinal product code	
Other name	Epivir
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

A single Lamivudine 150 mg tablet was administered orally, under fasting conditions at the start of each crossover period.

Number of subjects in period 1	All treated participants
Started	108
Completed	103
Not completed	5
Consent withdrawn by subject	4
Dismissed	1

Period 2

Period 2 title	Crossover Period 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Arm title	All treated participants

Arm description:

Participants were assigned to one of the following two crossover treatment sequences: one FDC tablet containing both Raltegravir and Lamivudine in Period 1; followed by individual Raltegravir and Lamivudine tablets in Period 2; or vice versa. Period 1 was separated from Period 2 by a minimum of 7 days washout. The population analysed was all participants who received at least one administration of study treatment.

Arm type	Experimental
Investigational medicinal product name	Raltegravir/lamivudine 300 mg/150 mg FDC tablets
Investigational medicinal product code	
Other name	MK-0518B
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

A single Raltegravir/lamivudine 300 mg/150 mg FDC tablet was administered orally, under fasting conditions at the start of each crossover period.

Investigational medicinal product name	Raltegravir
Investigational medicinal product code	
Other name	Isentress
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

A single Raltegravir 400 mg tablet was administered orally, under fasting conditions at the start of each crossover period.

Investigational medicinal product name	Lamivudine
Investigational medicinal product code	
Other name	Epivir
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

A single Lamivudine 150 mg tablet was administered orally, under fasting conditions at the start of each crossover period.

Number of subjects in period 2	All treated participants
Started	103
Completed	103

Baseline characteristics

Reporting groups	
Reporting group title	Crossover Period 1

Reporting group description: -

Reporting group values	Crossover Period 1	Total	
Number of subjects	108	108	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	35		
standard deviation	± 10	-	
Gender categorical Units: Subjects			
Female	55	55	
Male	53	53	

End points

End points reporting groups

Reporting group title	All treated participants

Reporting group description:

Participants were assigned to one of the following two crossover treatment sequences: one FDC tablet containing both Raltegravir and Lamivudine in Period 1; followed by individual Raltegravir and Lamivudine tablets in Period 2; or vice versa. Period 1 was separated from Period 2 by a minimum of 7 days washout. The population analysed was all participants who received at least one administration of study treatment.

Reporting group title	All treated participants

Reporting group description:

Participants were assigned to one of the following two crossover treatment sequences: one FDC tablet containing both Raltegravir and Lamivudine in Period 1; followed by individual Raltegravir and Lamivudine tablets in Period 2; or vice versa. Period 1 was separated from Period 2 by a minimum of 7 days washout. The population analysed was all participants who received at least one administration of study treatment.

Subject analysis set title	Single Raltegravir/lamivudine 300 mg/150 mg FDC tablet
Subject analysis set type	Per protocol

Subject analysis set description:

Participants were treated with one FDC tablet containing both Raltegravir and Lamivudine. The pharmacokinetic population analyzed had a sufficient set of samples in at least one study period, to provide enough data to estimate a particular endpoint.

Subject analysis set title	Separate Raltegravir 400 mg and Lamivudine 150 mg tablets
Subject analysis set type	Per protocol

Subject analysis set description:

Participants were treated with individual Raltegravir and Lamivudine tablets.The pharmacokinetic population analyzed had a sufficient set of samples in at least one study period, to provide enough data to estimate a particular endpoint.

Primary: Area under the plasma concentration time curve from time 0 to last time with quantifiable drug (AUC 0-t) of Raltegravir and Lamivudine

End point title	Area under the plasma concentration time curve from time 0 to last time with quantifiable drug (AUC 0-t) of Raltegravir and Lamivudine

End point description:

Participants were treated with a single FDC tablet or two separate tablets. Blood samples were obtained at the following time-points: predose, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, and 48 hours post-dose in order to determine the AUC 0-t of raltegravir and lamivudine.

End point type	Primary

End point timeframe:

Pre-dose, and from 0.5 to 48 hours post-dose

End point values	Single Raltegravir/lamivudine 300 mg/150 mg FDC tablet	Separate Raltegravir 400 mg and Lamivudine 150 mg tablets		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	106	103		
Units: hr.ng./mL				
geometric mean (confidence interval 95%)				

Raltegravir	8706.03 (8142.17 to 9308.93)	8622.42 (7628.48 to 9745.86)		
Lamivudine	5946.8 (5677.7 to 6228.7)	6048.9 (5796 to 6314.9)		

Statistical analyses

Statistical analysis title	Geom. Mean Ratio (GMR) % FDC vs Separate - Ralt

Statistical analysis description:

Based on log-transformed data, and using a linear mixed effects model. The linear mixed-effect model contained period and treatment as fixed effects. An unstructured covariance matrix was used to allow for unequal treatment variances and to model the correlation between the two treatment measurements within each participant. The number of participants treated with a single FDC tablet = 106; number treated with two separate tablets = 103.

Comparison groups	Single Raltegravir/lamivudine 300 mg/150 mg FDC tablet v Separate Raltegravir 400 mg and Lamivudine 150 mg tablets
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	equivalence[1]
Parameter estimate	GMR %
Point estimate	100.97
Confidence interval	
level	90 %
sides	2-sided
lower limit	92.46
upper limit	110.27

Notes:

[1] - The 90% confidence interval (CI) of the GMR % (FDC/Individual tablets) should be between 80 and 125%.

Statistical analysis title	GMR % FDC vs Separate - Lami

Statistical analysis description:

Based on log-transformed data, and using a linear mixed effects model. The linear mixed-effect model contained period and treatment as fixed effects. An unstructured covariance matrix was used to allow for unequal treatment variances and to model the correlation between the two treatment measurements within each participant. The number of participants treated with a single FDC tablet = 106; number treated with two separate tablets = 103.

Comparison groups	Single Raltegravir/lamivudine 300 mg/150 mg FDC tablet v Separate Raltegravir 400 mg and Lamivudine 150 mg tablets
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	equivalence[2]
Parameter estimate	GMR %
Point estimate	98.3
Confidence interval	
level	90 %
sides	2-sided
lower limit	96.03
upper limit	100.62

Notes:

[2] - The 90% CI of the GMR % (FDC/Individual tablets) should be between 80 and 125%

Primary: Area under the plasma concentration time curve from time 0 to infinity (AUC 0-inf) of Raltegravir and Lamivudine

End point title	Area under the plasma concentration time curve from time 0 to infinity (AUC 0-inf) of Raltegravir and Lamivudine

End point description:

Participants were treated with a single FDC tablet or two separate tablets. Blood samples were obtained at the following time-points: predose, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, and 48 hours post-dose in order to determine the AUC 0-inf of raltegravir and lamivudine.

End point type	Primary

End point timeframe:

Pre-dose, and 0.5 to 48 hours post-dose

End point values	Single Raltegravir/lamivudine 300 mg/150 mg FDC tablet	Separate Raltegravir 400 mg and Lamivudine 150 mg tablets		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	106	102		
Units: hr.ng./mL				
geometric mean (confidence interval 95%)				
Raltegravir (n = 103, 98)	8852.32 (8267.17 to 9478.89)	9019.93 (7921.1 to 10271.19)		
Lamivudine (n = 106, 102)	6104 (5833.4 to 6387.2)	6201.2 (5947.4 to 6465.8)		

Statistical analyses

Statistical analysis title	GMR % one FDC vs two separate tablets - Ralt

Statistical analysis description:

Based on log-transformed data, and using a linear mixed effects model. The linear mixed-effect model contained period and treatment as fixed effects. An unstructured covariance matrix was used to allow for unequal treatment variances and to model the correlation between the two treatment measurements within each participant. The number of participants treated with a single FDC tablet = 106; number treated with two separate tablets = 102.

Comparison groups	Single Raltegravir/lamivudine 300 mg/150 mg FDC tablet v Separate Raltegravir 400 mg and Lamivudine 150 mg tablets
Number of subjects included in analysis	208
Analysis specification	Pre-specified
Analysis type	equivalence[3]
Parameter estimate	GMR %
Point estimate	98.14

Confidence interval	
level	90 %
sides	2-sided
lower limit	89.48
upper limit	107.65

Notes:

[3] - The 90% CI of the GMR % (FDC/Individual tablets) is presented.

Statistical analysis title	GMR % one FDC vs two separate tablets - Lami

Statistical analysis description:

Based on log-transformed data, and using a linear mixed effects model. The linear mixed-effect model contained period and treatment as fixed effects. An unstructured covariance matrix was used to allow for unequal treatment variances and to model the correlation between the two treatment measurements within each participant. The number of participants treated with a single FDC tablet = 106; number treated with two separate tablets = 102.

Comparison groups	Single Raltegravir/lamivudine 300 mg/150 mg FDC tablet v Separate Raltegravir 400 mg and Lamivudine 150 mg tablets
Number of subjects included in analysis	208
Analysis specification	Pre-specified
Analysis type	equivalence[4]
Parameter estimate	GMR %
Point estimate	98.43
Confidence interval	
level	90 %
sides	2-sided
lower limit	96.32
upper limit	100.59

Notes:

[4] - The 90% CI of the GMR % (FDC/Individual tablets) is presented.

Primary: Plasma concentration at 12 hours post-dose (C12hr) of Raltegravir

End point title	Plasma concentration at 12 hours post-dose (C12hr) of Raltegravir

End point description:

Participants were treated with a single FDC tablet or two separate tablets. Blood samples were obtained at 12 hours post-dose in order to determine the C12hr of raltegravir.

End point type	Primary

End point timeframe:

12 hours post-dose

End point values	Single Raltegravir/lamivudine 300 mg/150 mg FDC tablet	Separate Raltegravir 400 mg and Lamivudine 150 mg tablets		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	106	103		
Units: ng/mL				
geometric mean (confidence interval 95%)	36.55 (33 to 40.49)	42.94 (38.63 to 47.73)		

Statistical analyses

Statistical analysis title	GMR % one FDC vs two separate tablets - Ralt

Statistical analysis description:

Based on log-transformed data, and using a linear mixed effects model. The linear mixed-effect model contained period and treatment as fixed effects. An unstructured covariance matrix was used to allow for unequal treatment variances and to model the correlation between the two treatment measurements within each participant. The number of participants treated with a single FDC tablet = 106; number treated with two separate tablets = 103.

Comparison groups	Single Raltegravir/lamivudine 300 mg/150 mg FDC tablet v Separate Raltegravir 400 mg and Lamivudine 150 mg tablets
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	equivalence[5]
Parameter estimate	GMR %
Point estimate	85.12
Confidence interval	
level	90 %
sides	2-sided
lower limit	78.69
upper limit	92.07

Notes:

[5] - The 90% CI of the GMR % (FDC/Individual tablets) should be between 80 and 200%.

Primary: Maximum plasma concentration (Cmax) of Lamivudine

End point title	Maximum plasma concentration (Cmax) of Lamivudine

End point description:

Participants were treated with a single FDC tablet or two separate tablets. Blood samples were obtained at the following time-points: predose, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, and 48 hours post-dose in order to determine the Cmax of lamivudine.

End point type	Primary

End point timeframe:

Pre-dose, and 0.5 to 48 hours post-dose

End point values	Single Raltegravir/lamivudine 300 mg/150 mg FDC tablet	Separate Raltegravir 400 mg and Lamivudine 150 mg tablets		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	106	103		
Units: ng/mL				
geometric mean (confidence interval 95%)	1241.2 (1167.8 to 1319.2)	1226.3 (1159.4 to 1297)		

Statistical analyses

Statistical analysis title	GMR % one FDC vs two separate tablets - Lami

Statistical analysis description:

Based on log-transformed data, and using a linear mixed effects model. The linear mixed-effect model contained period and treatment as fixed effects. An unstructured covariance matrix was used to allow for unequal treatment variances and to model the correlation between the two treatment measurements within each participant. The number of participants treated with a single FDC tablet = 106; number treated with two separate tablets = 103.

Comparison groups	Single Raltegravir/lamivudine 300 mg/150 mg FDC tablet v Separate Raltegravir 400 mg and Lamivudine 150 mg tablets
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	equivalence[6]
Parameter estimate	GMR %
Point estimate	101.22
Confidence interval	
level	90 %
sides	2-sided
lower limit	97.19
upper limit	105.41

Notes:

[6] - The 90% CI of the GMR % (FDC/Individual tablets) should be between 80 and 125%

Primary: Time to maximum plasma concentration (Tmax) of Raltegravir and Lamivudine

End point title	Time to maximum plasma concentration (Tmax) of Raltegravir and Lamivudine[7]

End point description:

Participants were treated with a single FDC tablet or two separate tablets. Blood samples were obtained at the following time-points: predose, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, and 48 hours post-dose in order to determine the Tmax of raltegravir and lamivudine.

End point type	Primary

End point timeframe:

Pre-dose, and 0.5 to 48 hours post-dose

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only summary statistics are provided. Statistical comparisons between arms were neither planned nor performed for this primary endpoint.

End point values	Single Raltegravir/lamivudine 300 mg/150 mg FDC tablet	Separate Raltegravir 400 mg and Lamivudine 150 mg tablets		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	106	103		
Units: hrs.				

median (full range (min-max))				
Raltegravir	1 (0.5 to 4)	2 (0.5 to 6)		
Lamivudine	2 (0.5 to 4)	1 (0.5 to 4)		

Statistical analyses

No statistical analyses for this end point

Primary: Apparent elimination half-life (t1/2) of Raltegravir and Lamivudine

End point title	Apparent elimination half-life (t1/2) of Raltegravir and Lamivudine[8]

End point description:

Participants were treated with a single FDC tablet or two separate tablets. Blood samples were obtained at the following time-points: predose, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, and 48 hours post-dose in order to determine the t1/2 of raltegravir and lamivudine.

End point type	Primary

End point timeframe:

Pre-dose, and 0.5 to 48 hours post-dose

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only summary statistics are provided. Statistical comparisons between arms were neither planned nor performed for this primary endpoint.

End point values	Single Raltegravir/lamivudine 300 mg/150 mg FDC tablet	Separate Raltegravir 400 mg and Lamivudine 150 mg tablets		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	106	102		
Units: hrs.				
geometric mean (geometric coefficient of variation)				
Raltegravir (n = 103, 98)	11.2 (± 69.5)	12.1 (± 69.4)		
Lamivudine (n = 106, 102)	7.4 (± 57.3)	7.5 (± 58.5)		

Statistical analyses

No statistical analyses for this end point

Primary: Apparent terminal first order elimination rate constant (Kel) of Raltegravir and Lamivudine

End point title	Apparent terminal first order elimination rate constant (Kel) of Raltegravir and Lamivudine[9]

End point description:

Participants were treated with a single FDC tablet or two separate tablets. Blood samples were obtained at the following time-points: predose, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, and 48 hours post-dose in order to determine the Kel of raltegravir and lamivudine.

End point type	Primary

End point timeframe:

Pre-dose, and 0.5 to 48 hours post-dose

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only summary statistics are provided. Statistical comparisons between arms were neither planned nor performed for this primary endpoint.

End point values	Single Raltegravir/lamivudine 300 mg/150 mg FDC tablet	Separate Raltegravir 400 mg and Lamivudine 150 mg tablets		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	106	102		
Units: 1/hr.				
arithmetic mean (standard deviation)				
Raltegravir (n = 103, 98)	0.073 (± 0.0391)	0.067 (± 0.0349)		
Lamivudine (n = 106, 102)	0.1052 (± 0.0429)	0.1037 (± 0.0403)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 14 days after receiving the last treatment

Adverse event reporting additional description:

Participants were assigned to one of the following two crossover treatment sequences: one FDC tablet containing both Raltegravir and Lamivudine in Period 1; followed by individual Raltegravir and Lamivudine tablets in Period 2; or vice versa. The population analysed was all participants who received at least one administration of study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups

Reporting group title	Single Raltegravir/lamivudine 300 mg/150 mg FDC tablet

Reporting group description:

Participants who received a single Raltegravir/lamivudine 300 mg/150 mg FDC tablet during each treatment period.

Reporting group title	Separate Raltegravir 400 mg and Lamivudine 150 mg tablets

Reporting group description:

Participants who received separate Raltegravir 400 mg and Lamivudine 150 mg tablets during each treatment period.

Serious adverse events	Single Raltegravir/lamivudine 300 mg/150 mg FDC tablet	Separate Raltegravir 400 mg and Lamivudine 150 mg tablets	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 107 (0.00%)	0 / 104 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Single Raltegravir/lamivudine 300 mg/150 mg FDC tablet	Separate Raltegravir 400 mg and Lamivudine 150 mg tablets	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 107 (11.21%)	10 / 104 (9.62%)	
Nervous system disorders			
Headache			
subjects affected / exposed	12 / 107 (11.21%)	10 / 104 (9.62%)	
occurrences (all)	12	12	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported