



## Clinical trial results: MK-0518B Food Effect Study Summary

EudraCT number	2014-004766-15
Trial protocol	Outside EU/EEA
Global end of trial date	02 November 2012

### Results information

Result version number	v1 (current)
This version publication date	15 March 2016
First version publication date	19 July 2015

### Trial information

#### Trial identification

Sponsor protocol code	MK-0518B-254
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#### 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)	EMA-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:

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**Results analysis stage**

Analysis stage	Final
Date of interim/final analysis	02 November 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 November 2012
Global end of trial reached?	Yes
Global end of trial date	02 November 2012
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

Main objective of the trial:

This study aimed to assess the effect of a high-fat meal on the in vivo performance of Raltegravir/lamivudine (MK-0518B) 300 mg/150 mg Fixed-Dose Combination (FDC) tablets after a single-dose in healthy participants.

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	15 October 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

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**Population of trial subjects****Subjects enrolled per country**

Country: Number of subjects enrolled	Canada: 20
Worldwide total number of subjects	20
EEA total number of subjects	0

Notes:

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**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)	20
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)  $\geq 19.0$  and  $\leq 30.0$  kg/m<sup>2</sup> 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
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Arm description:

Participants were assigned to one of the following two crossover treatment sequences: Period 1 was an overnight fast of at least 10 hours prior to drug administration; followed by Period 2 with a standardized high fat, high calorie breakfast 30 minutes prior to drug administration; or vice versa. In both periods participants were given a single oral treatment of raltegravir 300 mg/ lamivudine 150 mg fixed-dose combination (FDC) tablet. Period 1 was separated from Period 2 by a 7 day 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, at the start of each crossover period.

<b>Number of subjects in period 1</b>	All treated participants
Started	20
Completed	20

### Period 2

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

## Arms

<b>Arm title</b>	All treated participants
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### Arm description:

Participants were assigned to one of the following two crossover treatment sequences: Period 1 was an overnight fast of at least 10 hours prior to drug administration; followed by Period 2 with a standardized high fat, high calorie breakfast 30 minutes prior to drug administration; or vice versa. In both periods participants were given a single oral treatment of raltegravir 300 mg/ lamivudine 150 mg fixed-dose combination (FDC) tablet. Period 1 was separated from Period 2 by a 7 day 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, at the start of each crossover period.

<b>Number of subjects in period 2</b>	All treated participants
Started	20
Completed	20

## Baseline characteristics

### Reporting groups

Reporting group title	Crossover Period 1
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Reporting group description:

Participants were assigned to one of the following two crossover treatment sequences: Period 1 was an overnight fast of at least 10 hours prior to drug administration; followed by Period 2 with a standardized high fat, high calorie breakfast 30 minutes prior to drug administration; or vice versa. In both periods participants were given a single oral treatment of raltegravir 300 mg/ lamivudine 150 mg fixed-dose combination (FDC) tablet.

Reporting group values	Crossover Period 1	Total	
Number of subjects	20	20	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	42 ± 8	-	
Gender categorical Units: Subjects			
Female	12	12	
Male	8	8	

## End points

### End points reporting groups

Reporting group title	All treated participants
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Reporting group description:

Participants were assigned to one of the following two crossover treatment sequences: Period 1 was an overnight fast of at least 10 hours prior to drug administration; followed by Period 2 with a standardized high fat, high calorie breakfast 30 minutes prior to drug administration; or vice versa. In both periods participants were given a single oral treatment of raltegravir 300 mg/ lamivudine 150 mg fixed-dose combination (FDC) tablet. Period 1 was separated from Period 2 by a 7 day washout. The population analysed was all participants who received at least one administration of study treatment.

Reporting group title	All treated participants
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Reporting group description:

Participants were assigned to one of the following two crossover treatment sequences: Period 1 was an overnight fast of at least 10 hours prior to drug administration; followed by Period 2 with a standardized high fat, high calorie breakfast 30 minutes prior to drug administration; or vice versa. In both periods participants were given a single oral treatment of raltegravir 300 mg/ lamivudine 150 mg fixed-dose combination (FDC) tablet. Period 1 was separated from Period 2 by a 7 day washout. The population analysed was all participants who received at least one administration of study treatment.

Subject analysis set title	Fasted + FDC Treatment
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Subject analysis set type	Per protocol
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Subject analysis set description:

Participants had a 10 hour overnight fast prior to treatment with a single FDC tablet containing 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	High Fat Meal + FDC Treatment
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Subject analysis set type	Per protocol
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Subject analysis set description:

Participants had a high fat, high calorie breakfast 30 minutes prior to treatment with a single FDC tablet containing 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..

### 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
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End point description:

Participants were treated with a single FDC tablet, then 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
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End point timeframe:

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

End point values	Fasted + FDC Treatment	High Fat Meal + FDC Treatment		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	20		
Units: hr.ng./mL				
geometric mean (confidence interval 95%)				

Raltegravir	8381.74 (7036.95 to 9983.52)	7918.47 (7031.92 to 8916.8)		
Lamivudine	6654.9 (6081.8 to 7282)	6152.5 (5648.8 to 6701.2)		

## Statistical analyses

<b>Statistical analysis title</b>	Geom. Mean Ratio (GMR) % Fasted vs Meal - Ralt
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Statistical analysis description:

Based on log-transformed data, and using a linear mixed effects model. The correct number of participants in this analysis is not 40, but 20: the number of participants in this analysis who were fasted was 20, and the same 20 participants received a high fat meal.

Comparison groups	Fasted + FDC Treatment v High Fat Meal + FDC Treatment
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other <sup>[1]</sup>
Parameter estimate	GMR %
Point estimate	94.47
Confidence interval	
level	90 %
sides	2-sided
lower limit	83.37
upper limit	107.05

Notes:

[1] - GMR % (Fed/Fasted) was estimated; did not include any pre-specified bounds.

<b>Statistical analysis title</b>	GMR % Fasted vs Meal - Lami
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Statistical analysis description:

Based on log-transformed data, and using a linear mixed effects model. The correct number of participants in this analysis is not 40, but 20: the number of participants in this analysis who were fasted was 20, and the same 20 participants received a high fat meal.

Comparison groups	Fasted + FDC Treatment v High Fat Meal + FDC Treatment
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other <sup>[2]</sup>
Parameter estimate	GMR %
Point estimate	92.45
Confidence interval	
level	90 %
sides	2-sided
lower limit	87.23
upper limit	97.98

Notes:

[2] - GMR % (Fed/Fasted) was estimated; did not include any pre-specified bounds.

## 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
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**End point description:**

Participants were treated with a single FDC tablet, then 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
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**End point timeframe:**

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

End point values	Fasted + FDC Treatment	High Fat Meal + FDC Treatment		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	20		
Units: hr.ng./mL				
geometric mean (confidence interval 95%)				
Raltegravir (n = 20, 19)	8603.28 (7235.11 to 10230.16)	8106.17 (7138.5 to 9205.02)		
Lamivudine (n = 20, 20)	6834 (6241.7 to 7482.6)	6316.8 (5786.3 to 6896)		

**Statistical analyses**

<b>Statistical analysis title</b>	GMR % Fasted vs Meal - Ralt
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**Statistical analysis description:**

Based on log-transformed data, and using a linear mixed effects model. The correct number of participants in this analysis is not 40, but 20: the number of participants in this analysis who were fasted was 20, and the same 20 participants received a high fat meal.

Comparison groups	High Fat Meal + FDC Treatment v Fasted + FDC Treatment
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other <sup>[3]</sup>
Parameter estimate	GMR %
Point estimate	94.22
Confidence interval	
level	90 %
sides	2-sided
lower limit	82.93
upper limit	107.05

**Notes:**

[3] - GMR % (Fed/Fasted) was estimated; did not include any pre-specified bounds.

<b>Statistical analysis title</b>	GMR % Fasted vs Meal - Lami
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**Statistical analysis description:**

Based on log-transformed data, and using a linear mixed effects model. The correct number of participants in this analysis is not 40, but 20: the number of participants in this analysis who were fasted was 20, and the same 20 participants received a high fat meal.

Comparison groups	Fasted + FDC Treatment v High Fat Meal + FDC Treatment
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Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other <sup>[4]</sup>
Parameter estimate	GMR %
Point estimate	92.43
Confidence interval	
level	90 %
sides	2-sided
lower limit	87.51
upper limit	97.63

Notes:

[4] - GMR % (Fed/Fasted) was estimated; did not include any pre-specified bounds.

### Primary: Maximum plasma concentration (Cmax) of Raltegravir and Lamivudine

End point title	Maximum plasma concentration (Cmax) of Raltegravir and Lamivudine
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End point description:

Participants were treated with a single FDC tablet, then 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 raltegravir and lamivudine.

End point type	Primary
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End point timeframe:

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

End point values	Fasted + FDC Treatment	High Fat Meal + FDC Treatment		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	20		
Units: ng/mL				
geometric mean (confidence interval 95%)				
Raltegravir	2874.04 (2101.69 to 3930.22)	2212.79 (1705.78 to 2870.51)		
Lamivudine	1358 (1172.7 to 1572.6)	1078.7 (918.5 to 1266.7)		

### Statistical analyses

Statistical analysis title	GMR % Fasted vs Meal - Ralt
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Statistical analysis description:

Based on log-transformed data, and using a linear mixed effects model. The correct number of participants in this analysis is not 40, but 20: the number of participants in this analysis who were fasted was 20, and the same 20 participants received a high fat meal.

Comparison groups	Fasted + FDC Treatment v High Fat Meal + FDC Treatment
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Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other <sup>[5]</sup>
Parameter estimate	GMR %
Point estimate	76.99
Confidence interval	
level	90 %
sides	2-sided
lower limit	55.16
upper limit	107.46

Notes:

[5] - GMR % (Fed/Fasted) was estimated; did not include any pre-specified bounds.

<b>Statistical analysis title</b>	GMR % Fasted vs Meal - Lami
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Statistical analysis description:

Based on log-transformed data, and using a linear mixed effects model. The correct number of participants in this analysis is not 40, but 20: the number of participants in this analysis who were fasted was 20, and the same 20 participants received a high fat meal.

Comparison groups	Fasted + FDC Treatment v High Fat Meal + FDC Treatment
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other <sup>[6]</sup>
Parameter estimate	GMR %
Point estimate	79.43
Confidence interval	
level	90 %
sides	2-sided
lower limit	70.73
upper limit	89.2

Notes:

[6] - GMR % (Fed/Fasted) was estimated; did not include any pre-specified bounds.

### **Primary: Plasma concentration at 12 hours post-dose (C12hr) of Raltegravir and Lamivudine**

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

Participants were treated with a single FDC tablet, then blood samples were obtained at 12 hours post-dose in order to determine the C12hr of raltegravir and lamivudine.

End point type	Primary
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End point timeframe:

12 hours post-dose

End point values	Fasted + FDC Treatment	High Fat Meal + FDC Treatment		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	20		
Units: ng/mL				
geometric mean (confidence interval 95%)				
Raltegravir	37.31 (30.33 to 45.9)	44.82 (31.99 to 62.8)		
Lamivudine	77.4 (68.8 to 87.2)	118.2 (97.9 to 142.6)		

## Statistical analyses

Statistical analysis title	GMR % Fasted vs Meal - Ralt
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Statistical analysis description:

Based on log-transformed data, and using a linear mixed effects model. The correct number of participants in this analysis is not 40, but 20: the number of participants in this analysis who were fasted was 20, and the same 20 participants received a high fat meal.

Comparison groups	Fasted + FDC Treatment v High Fat Meal + FDC Treatment
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other <sup>[7]</sup>
Parameter estimate	GMR %
Point estimate	120.14
Confidence interval	
level	90 %
sides	2-sided
lower limit	89.48
upper limit	161.3

Notes:

[7] - GMR % (Fed/Fasted) was estimated; did not include any pre-specified bounds.

Statistical analysis title	GMR Fasted vs Meal - Lami
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Statistical analysis description:

Based on log-transformed data, and using a linear mixed effects model. The correct number of participants in this analysis is not 40, but 20: the number of participants in this analysis who were fasted was 20, and the same 20 participants received a high fat meal.

Comparison groups	Fasted + FDC Treatment v High Fat Meal + FDC Treatment
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other <sup>[8]</sup>
Parameter estimate	GMR %
Point estimate	152.62
Confidence interval	
level	90 %
sides	2-sided
lower limit	134.47
upper limit	173.22

Notes:

[8] - GMR % (Fed/Fasted) was estimated; did not include any pre-specified bounds.

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

End point title	Time to maximum plasma concentration (Tmax) of Raltegravir and Lamivudine <sup>[9]</sup>
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End point description:

Participants were treated with a single FDC tablet, then 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
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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	Fasted + FDC Treatment	High Fat Meal + FDC Treatment		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	20		
Units: hr				
median (full range (min-max))				
Raltegravir	1 (0.5 to 4)	3 (2 to 8)		
Lamivudine	2 (1 to 3)	4 (2 to 8)		

### 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 <sup>[10]</sup>
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End point description:

Participants were treated with a single FDC tablet, then 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
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End point timeframe:

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

Notes:

[10] - 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	Fasted + FDC Treatment	High Fat Meal + FDC Treatment		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	20		
Units: hr.				
geometric mean (geometric coefficient of variation)				
Raltegravir (n = 20, 19)	14.1 (± 69.7)	13 (± 88.9)		
Lamivudine (n = 20, 20)	6.8 (± 64.4)	8.3 (± 52.4)		

## 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 <sup>[11]</sup>
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End point description:

Participants were treated with a single FDC tablet, then 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
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End point timeframe:

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

Notes:

[11] - 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	Fasted + FDC Treatment	High Fat Meal + FDC Treatment		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	20		
Units: 1/hr.				
arithmetic mean (standard deviation)				
Raltegravir (n = 20, 19)	0.0594 (± 0.0412)	0.0712 (± 0.0609)		
Lamivudine (n = 20, 20)	0.1174 (± 0.0595)	0.0926 (± 0.0406)		

## 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 in Period 2 (up to Day 25).

Adverse event reporting additional description:

Period 1 was a 10 hour overnight fast prior to drug; Period 2 was a high fat, high calorie breakfast 30 minutes prior to drug; or vice versa. Participants were given a single FDC tablet containing raltegravir and lamivudine in both periods. The population analysed was all participants who received at least one administration of study treatment.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	15.1
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### Reporting groups

Reporting group title	Fasted + FDC Treatment
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Reporting group description:

Participants had a 10 hour overnight fast prior to treatment with a single FDC tablet containing raltegravir and lamivudine. The population analysed was all participants who received at least one administration of study treatment.

Reporting group title	High Fat Meal + FDC Treatment
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Reporting group description:

Participants had a high fat, high calorie breakfast 30 minutes prior to treatment with a single FDC tablet containing raltegravir and lamivudine. The population analysed was all participants who received at least one administration of study treatment.

Serious adverse events	Fasted + FDC Treatment	High Fat Meal + FDC Treatment	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (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	Fasted + FDC Treatment	High Fat Meal + FDC Treatment	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 20 (5.00%)	3 / 20 (15.00%)	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 20 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Headache			

subjects affected / exposed	1 / 20 (5.00%)	2 / 20 (10.00%)	
occurrences (all)	1	2	

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported