



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 | v2 (current) |
| This version publication date | 09 April 2016 |
| First version publication date | 19 July 2015 |
| Version creation reason | |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | 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 (AUC_{0-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 (C_{12hr}) 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 AUC_{0-t} and the maximum plasma concentration (C_{max}) 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 months) | 0 |

| | |
|---------------------------|-----|
| 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/m² 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 | 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.

| | |
|--|-------------|
| 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.

| 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 | 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.

| | |
|--|-------------|
| 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.

| 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 standard deviation | 35 ± 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) | 6049.9 (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 (C_{max}) of Lamivudine

| | |
|--|--|
| End point title | Maximum plasma concentration (C _{max}) 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 C _{max} 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 (t_{1/2}) of Raltegravir and Lamivudine

| | |
|-----------------|---|
| End point title | Apparent elimination half-life (t _{1/2}) 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 t_{1/2} 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