



Clinical trial results:

A Phase 1 Relative Bioavailability and Food Effect Study of a Pediatric Oral Granule Formulation of Ledipasvir/Sofosbuvir in Healthy Adult Subjects

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2017-003956-22 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 27 July 2016 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 06 December 2017 |
| First version publication date | 06 December 2017 |

Trial information

Trial identification

| | |
|-----------------------|----------------|
| Sponsor protocol code | GS-US-337-2091 |
|-----------------------|----------------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Gilead Sciences |
| Sponsor organisation address | 333 Lakeside Drive, Foster City, CA, United States, 94404 |
| Public contact | Clinical Trials Mailbox , Gilead Sciences International Ltd , ClinicalTrialDisclosures@gilead.com |
| Scientific contact | Clinical Trials Mailbox , Gilead Sciences International Ltd , ClinicalTrialDisclosures@gilead.com |

Notes:

Paediatric regulatory details

| | |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMA-001411-PIP01-12 |
| 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 | 27 July 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 27 July 2016 |
| Global end of trial reached? | Yes |
| Global end of trial date | 27 July 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of this study were to evaluate the relative bioavailability of a pediatric oral granule formulation of ledipasvir/sofosbuvir (LDV/SOF) relative to tablet formulation in healthy participants and to evaluate the effect of concomitant food intake on the pharmacokinetics (PK) of a pediatric oral granule formulation of LDV/SOF.

Protection of trial subjects:

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

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

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------|
| Actual start date of recruitment | 24 May 2016 |
| 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 | United States: 42 |
| Worldwide total number of subjects | 42 |
| 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) | 42 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at one study site in the United States. The first participant was screened on 24 May 2016. The last study visit occurred on 27 July 2016.

Pre-assignment

Screening details:

58 participants were screened.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|---------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Treatment ABC |

Arm description:

Treatment A, 9-day washout, Treatment B, 9-day washout, and then Treatment C.

| | |
|--|------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Ledipasvir/sofosbuvir |
| Investigational medicinal product code | |
| Other name | LDV/SOF, Harvoni®, GS-5885/GS-7977 |
| Pharmaceutical forms | Granules, Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Treatment A = Single dose of LDV/SOF (90/400 mg tablet) under fasted condition

Treatment B = Single dose of LDV/SOF (8 x 11.25/50 mg oral granules) under fasted condition

Treatment C = Single dose of LDV/SOF (8 x 11.25/50 mg oral granules) under fed condition

| | |
|------------------|---------------|
| Arm title | Treatment ACB |
|------------------|---------------|

Arm description:

Treatment A, 9-day washout, Treatment C, 9-day washout, and then Treatment B.

| | |
|--|------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Ledipasvir/sofosbuvir |
| Investigational medicinal product code | |
| Other name | LDV/SOF, Harvoni®, GS-5885/GS-7977 |
| Pharmaceutical forms | Granules, Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Treatment A = Single dose of LDV/SOF (90/400 mg tablet) under fasted condition

Treatment C = Single dose of LDV/SOF (8 x 11.25/50 mg oral granules) under fed condition

Treatment B = Single dose of LDV/SOF (8 x 11.25/50 mg oral granules) under fasted condition

| | |
|------------------|---------------|
| Arm title | Treatment BCA |
|------------------|---------------|

Arm description:

Treatment B, 9-day washout, Treatment C, 9-day washout, and then Treatment A.

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|------------------------------------|
| Investigational medicinal product name | Ledipasvir/sofosbuvir |
| Investigational medicinal product code | |
| Other name | LDV/SOF, Harvoni®, GS-5885/GS-7977 |
| Pharmaceutical forms | Granules, Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Treatment B = Single dose of LDV/SOF (8 x 11.25/50 mg oral granules) under fasted condition

Treatment C = Single dose of LDV/SOF (8 x 11.25/50 mg oral granules) under fed condition

Treatment A = Single dose of LDV/SOF (90/400 mg tablet) under fasted condition

| | |
|------------------|---------------|
| Arm title | Treatment BAC |
|------------------|---------------|

Arm description:

Treatment B, 9-day washout, Treatment A, 9-day washout, and then Treatment C.

| | |
|--|------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Ledipasvir/sofosbuvir |
| Investigational medicinal product code | |
| Other name | LDV/SOF, Harvoni®, GS-5885/GS-7977 |
| Pharmaceutical forms | Granules, Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Treatment B = Single dose of LDV/SOF (8 x 11.25/50 mg oral granules) under fasted condition

Treatment A = Single dose of LDV/SOF (90/400 mg tablet) under fasted condition

Treatment C = Single dose of LDV/SOF (8 x 11.25/50 mg oral granules) under fed condition

| | |
|------------------|---------------|
| Arm title | Treatment CBA |
|------------------|---------------|

Arm description:

Treatment C, 9-day washout, Treatment B, 9-day washout, and then Treatment A.

| | |
|--|------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Ledipasvir/sofosbuvir |
| Investigational medicinal product code | |
| Other name | LDV/SOF, Harvoni®, GS-5885/GS-7977 |
| Pharmaceutical forms | Granules, Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Treatment C = Single dose of LDV/SOF (8 x 11.25/50 mg oral granules) under fed condition

Treatment B = Single dose of LDV/SOF (8 x 11.25/50 mg oral granules) under fasted condition

Treatment A = Single dose of LDV/SOF (90/400 mg tablet) under fasted condition

| | |
|------------------|---------------|
| Arm title | Treatment CAB |
|------------------|---------------|

Arm description:

Treatment C, 9-day washout, Treatment A, 9-day washout, and then Treatment B.

| | |
|--|------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Ledipasvir/sofosbuvir |
| Investigational medicinal product code | |
| Other name | LDV/SOF, Harvoni®, GS-5885/GS-7977 |
| Pharmaceutical forms | Granules, Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Treatment C = Single dose of LDV/SOF (8 x 11.25/50 mg oral granules) under fed condition

Treatment A = Single dose of LDV/SOF (90/400 mg tablet) under fasted condition

Treatment B = Single dose of LDV/SOF (8 x 11.25/50 mg oral granules) under fasted condition

| Number of subjects in period 1 | Treatment ABC | Treatment ACB | Treatment BCA |
|---------------------------------------|---------------|---------------|---------------|
| Started | 7 | 7 | 7 |
| Completed | 7 | 7 | 7 |

| Number of subjects in period 1 | Treatment BAC | Treatment CBA | Treatment CAB |
|---------------------------------------|---------------|---------------|---------------|
| Started | 7 | 7 | 7 |
| Completed | 7 | 7 | 7 |

Baseline characteristics

Reporting groups

| | |
|---|---------------|
| Reporting group title | Treatment ABC |
| Reporting group description: Treatment A, 9-day washout, Treatment B, 9-day washout, and then Treatment C. | |
| Reporting group title | Treatment ACB |
| Reporting group description: Treatment A, 9-day washout, Treatment C, 9-day washout, and then Treatment B. | |
| Reporting group title | Treatment BCA |
| Reporting group description: Treatment B, 9-day washout, Treatment C, 9-day washout, and then Treatment A. | |
| Reporting group title | Treatment BAC |
| Reporting group description: Treatment B, 9-day washout, Treatment A, 9-day washout, and then Treatment C. | |
| Reporting group title | Treatment CBA |
| Reporting group description: Treatment C, 9-day washout, Treatment B, 9-day washout, and then Treatment A. | |
| Reporting group title | Treatment CAB |
| Reporting group description: Treatment C, 9-day washout, Treatment A, 9-day washout, and then Treatment B. | |

| Reporting group values | Treatment ABC | Treatment ACB | Treatment BCA |
|------------------------------------|---------------|---------------|---------------|
| Number of subjects | 7 | 7 | 7 |
| Age categorical Units: Subjects | | | |

| | | | |
|---|-------------|-------------|-------------|
| Age continuous Units: years arithmetic mean standard deviation | 32 ± 7.4 | 29 ± 6.3 | 29 ± 4.8 |
| Gender categorical Units: Subjects | | | |
| Female | 1 | 2 | 2 |
| Male | 6 | 5 | 5 |
| Race Units: Subjects | | | |
| Black or African American | 3 | 3 | 3 |
| Native Hawaiian or Pacific Islander | 0 | 0 | 0 |
| White | 4 | 4 | 4 |
| Ethnicity Units: Subjects | | | |
| Hispanic or Latino | 5 | 6 | 4 |
| Not Hispanic or Latino | 2 | 1 | 3 |

| Reporting group values | Treatment BAC | Treatment CBA | Treatment CAB |
|------------------------|---------------|---------------|---------------|
| Number of subjects | 7 | 7 | 7 |

| | | | |
|---|-------------|-------------|-------------|
| Age categorical Units: Subjects | | | |
| Age continuous Units: years arithmetic mean standard deviation | 29 ± 6.4 | 26 ± 4.0 | 31 ± 6.3 |
| Gender categorical Units: Subjects | | | |
| Female | 2 | 3 | 2 |
| Male | 5 | 4 | 5 |
| Race Units: Subjects | | | |
| Black or African American | 2 | 4 | 3 |
| Native Hawaiian or Pacific Islander | 0 | 1 | 0 |
| White | 5 | 2 | 4 |
| Ethnicity Units: Subjects | | | |
| Hispanic or Latino | 5 | 4 | 4 |
| Not Hispanic or Latino | 2 | 3 | 3 |

| | | | |
|------------------------------------|-------|--|--|
| Reporting group values | Total | | |
| Number of subjects | 42 | | |
| Age categorical Units: Subjects | | | |

| | | | |
|---|----|--|--|
| Age continuous Units: years arithmetic mean standard deviation | - | | |
| Gender categorical Units: Subjects | | | |
| Female | 12 | | |
| Male | 30 | | |
| Race Units: Subjects | | | |
| Black or African American | 18 | | |
| Native Hawaiian or Pacific Islander | 1 | | |
| White | 23 | | |
| Ethnicity Units: Subjects | | | |
| Hispanic or Latino | 28 | | |
| Not Hispanic or Latino | 14 | | |

End points

End points reporting groups

| | |
|---|---------------|
| Reporting group title | Treatment ABC |
| Reporting group description: Treatment A, 9-day washout, Treatment B, 9-day washout, and then Treatment C. | |
| Reporting group title | Treatment ACB |
| Reporting group description: Treatment A, 9-day washout, Treatment C, 9-day washout, and then Treatment B. | |
| Reporting group title | Treatment BCA |
| Reporting group description: Treatment B, 9-day washout, Treatment C, 9-day washout, and then Treatment A. | |
| Reporting group title | Treatment BAC |
| Reporting group description: Treatment B, 9-day washout, Treatment A, 9-day washout, and then Treatment C. | |
| Reporting group title | Treatment CBA |
| Reporting group description: Treatment C, 9-day washout, Treatment B, 9-day washout, and then Treatment A. | |
| Reporting group title | Treatment CAB |
| Reporting group description: Treatment C, 9-day washout, Treatment A, 9-day washout, and then Treatment B. | |
| Subject analysis set title | Treatment A |
| Subject analysis set type | Per protocol |
| Subject analysis set description: Single dose of LDV/SOF (90/400 mg tablet) under fasted condition (Treatment A) | |
| Subject analysis set title | Treatment B |
| Subject analysis set type | Per protocol |
| Subject analysis set description: Single dose of LDV/SOF (8 x 11.25/50 mg oral granules) under fasted condition (Treatment B). | |
| Subject analysis set title | Treatment C |
| Subject analysis set type | Per protocol |
| Subject analysis set description: Single dose of LDV/SOF (8 x 11.25/50 mg oral granules) under fed condition (Treatment C) | |

Primary: Pharmacokinetic (PK) Parameter: Cmax of SOF, GS-566500, and GS-331007

| | |
|---|---|
| End point title | Pharmacokinetic (PK) Parameter: Cmax of SOF, GS-566500, and GS-331007 |
| End point description: Cmax is defined as the maximum concentration of drug. | |
| End point type | Primary |
| End point timeframe: Predose, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 20, 24, 48, 72, 96, 120 and 144 hours postdose | |

| End point values | Treatment A | Treatment B | Treatment C | |
|--------------------------------------|------------------------|------------------------|------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 42 | 42 | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| SOF | 1221.0 (\pm 469.99) | 1266.7 (\pm 589.77) | 1236.3 (\pm 605.60) | |
| GS-566500 | 475.1 (\pm 160.89) | 511.3 (\pm 178.63) | 593.9 (\pm 184.38) | |
| GS-331007 | 833.9 (\pm 197.11) | 951.9 (\pm 257.01) | 583.1 (\pm 141.01) | |

Statistical analyses

| Statistical analysis title | GLSM ratio of SOF (Treatment B vs A) |
|----------------------------|--------------------------------------|
|----------------------------|--------------------------------------|

Statistical analysis description:

Percentage geometric least-squares mean (GLSM) ratio is being presented. "Subjects in this analysis" states 84; however, only 42 unique participants were analyzed, each reported for Treatment B and Treatment A.

| | |
|---|------------------------------------|
| Comparison groups | Treatment B v Treatment A |
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[1] |
| Parameter estimate | Geometric least-squares mean ratio |
| Point estimate | 95.98 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 78 |
| upper limit | 118.11 |

Notes:

[1] - Statistical Comparison

| Statistical analysis title | GLSM ratio of SOF (Treatment C vs B) |
|----------------------------|--------------------------------------|
|----------------------------|--------------------------------------|

Statistical analysis description:

Percentage GLSM ratio is being presented. "Subjects in this analysis" states 84; however, only 42 unique participants were analyzed, each reported for Treatment C and Treatment B.

| | |
|---|------------------------------------|
| Comparison groups | Treatment C v Treatment B |
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[2] |
| Parameter estimate | Geometric least-squares mean ratio |
| Point estimate | 100.32 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 84.83 |
| upper limit | 118.65 |

Notes:

[2] - Statistical Comparison

| | |
|-----------------------------------|--|
| Statistical analysis title | GLSM ratio of GS-566500 (Treatment B vs A) |
|-----------------------------------|--|

Statistical analysis description:

Percentage GLSM ratio is being presented. "Subjects in this analysis" states 84; however, only 42 unique participants were analyzed, each reported for Treatment B and Treatment A.

| | |
|---|------------------------------------|
| Comparison groups | Treatment B v Treatment A |
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[3] |
| Parameter estimate | Geometric least-squares mean ratio |
| Point estimate | 103.04 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 91.06 |
| upper limit | 116.6 |

Notes:

[3] - Statistical Comparison

| | |
|-----------------------------------|--|
| Statistical analysis title | GLSM ratio of GS-566500 (Treatment C vs B) |
|-----------------------------------|--|

Statistical analysis description:

Percentage GLSM ratio is being presented. "Subjects in this analysis" states 84; however, only 42 unique participants were analyzed, each reported for Treatment C and Treatment B.

| | |
|---|------------------------------------|
| Comparison groups | Treatment C v Treatment B |
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[4] |
| Parameter estimate | Geometric least-squares mean ratio |
| Point estimate | 122.12 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 108.28 |
| upper limit | 137.73 |

Notes:

[4] - Statistical Comparison

| | |
|-----------------------------------|--|
| Statistical analysis title | GLSM ratio of GS-331007 (Treatment B vs A) |
|-----------------------------------|--|

Statistical analysis description:

Percentage GLSM ratio is being presented. "Subjects in this analysis" states 84; however, only 42 unique participants were analyzed, each reported for Treatment B and Treatment A.

| | |
|---|------------------------------------|
| Comparison groups | Treatment B v Treatment A |
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[5] |
| Parameter estimate | Geometric least-squares mean ratio |
| Point estimate | 112.81 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 104.12 |
| upper limit | 122.22 |

Notes:

[5] - Statistical Comparison

| | |
|-----------------------------------|--|
| Statistical analysis title | GLSM ratio of GS-331007 (Treatment C vs B) |
|-----------------------------------|--|

Statistical analysis description:

Percentage GLSM ratio is being presented. "Subjects in this analysis" states 84; however, only 42 unique participants were analyzed, each reported for Treatment C and Treatment B.

| | |
|---|------------------------------------|
| Comparison groups | Treatment C v Treatment B |
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[6] |
| Parameter estimate | Geometric least-squares mean ratio |
| Point estimate | 62.01 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 56.9 |
| upper limit | 67.59 |

Notes:

[6] - Statistical Comparison

Primary: PK Parameter: Cmax of LDV

| | |
|-----------------|---------------------------|
| End point title | PK Parameter: Cmax of LDV |
|-----------------|---------------------------|

End point description:

Cmax is defined as the maximum concentration of drug.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Predose, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 20, 24, 48, 72, 96, 120 and 144 hours postdose

| End point values | Treatment A | Treatment B | Treatment C | |
|--------------------------------------|----------------------|----------------------|----------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 39 ^[7] | 40 ^[8] | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | 261.3 (± 113.55) | 214.8 (± 82.05) | 159.8 (± 46.17) | |

Notes:

[7] - 3 participants were excluded since their LDV predose plasma concentration was > 5% of C_{max}.

[8] - 2 participants were excluded since their LDV predose plasma concentration was > 5% of C_{max}.

Statistical analyses

| Statistical analysis title | GLSM ratio of LDV (Treatment B vs A) |
|----------------------------|--------------------------------------|
|----------------------------|--------------------------------------|

Statistical analysis description:

Percentage GLSM ratio is being presented. "Subjects in this analysis" states 81; however, only 42 unique participants were analyzed, each reported for Treatment B (N = 39) and Treatment A (N = 42).

| | |
|---|------------------------------------|
| Comparison groups | Treatment B v Treatment A |
| Number of subjects included in analysis | 81 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[9] |
| Parameter estimate | Geometric least-squares mean ratio |
| Point estimate | 84.59 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 74.69 |
| upper limit | 95.81 |

Notes:

[9] - Statistical comparison

| Statistical analysis title | GLSM ratio of LDV (Treatment C vs B) |
|----------------------------|--------------------------------------|
|----------------------------|--------------------------------------|

Statistical analysis description:

Percentage GLSM ratio is being presented. "Subjects in this analysis" states 81; however, only 40 unique participants were analyzed, each reported for Treatment C (N = 40) and Treatment B (N = 39).

| | |
|---|------------------------------------|
| Comparison groups | Treatment C v Treatment B |
| Number of subjects included in analysis | 79 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[10] |
| Parameter estimate | Geometric least-squares mean ratio |
| Point estimate | 78.15 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 71.26 |
| upper limit | 85.71 |

Notes:

[10] - Statistical comparison

Primary: PK Parameter: AUClast of SOF, GS-566500, and GS-331007

| | |
|-----------------|--|
| End point title | PK Parameter: AUClast of SOF, GS-566500, and GS-331007 |
|-----------------|--|

End point description:

AUClast is defined as the concentration of drug from time zero to the last observable concentration.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Predose, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 20, 24, 48, 72, 96, 120 and 144 hours postdose

| End point values | Treatment A | Treatment B | Treatment C | |
|--------------------------------------|----------------------|----------------------|----------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 42 | 42 | |
| Units: h*ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| SOF | 1559.8 (± 632.08) | 1676.9 (± 732.07) | 2577.2 (± 852.76) | |
| GS-566500 | 1846.6 (± 579.71) | 1952.9 (± 654.54) | 2931.7 (± 559.29) | |
| GS-331007 | 11146.3 (± 2999.47) | 11525.8 (± 3037.01) | 11653.6 (± 2197.58) | |

Statistical analyses

| | |
|-----------------------------------|--------------------------------------|
| Statistical analysis title | GLSM ratio of SOF (Treatment B vs A) |
|-----------------------------------|--------------------------------------|

Statistical analysis description:

Percentage GLSM ratio is being presented. "Subjects in this analysis" states 84; however, only 42 unique participants were analyzed, each reported for Treatment B and Treatment A.

| | |
|---|------------------------------------|
| Comparison groups | Treatment B v Treatment A |
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[11] |
| Parameter estimate | Geometric least-squares mean ratio |
| Point estimate | 102.13 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 87.16 |
| upper limit | 119.67 |

Notes:

[11] - Statistical Comparison

| | |
|-----------------------------------|--------------------------------------|
| Statistical analysis title | GLSM ratio of SOF (Treatment C vs B) |
|-----------------------------------|--------------------------------------|

Statistical analysis description:

Percentage GLSM ratio is being presented. "Subjects in this analysis" states 84; however, only 42 unique participants were analyzed, each reported for Treatment C and Treatment B.

| | |
|-------------------|---------------------------|
| Comparison groups | Treatment C v Treatment B |
|-------------------|---------------------------|

| | |
|---|------------------------------------|
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[12] |
| Parameter estimate | Geometric least-squares mean ratio |
| Point estimate | 166.11 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 145 |
| upper limit | 190.3 |

Notes:

[12] - Statistical Comparison

| | |
|-----------------------------------|--|
| Statistical analysis title | GLSM ratio of GS-566500 (Treatment B vs A) |
|-----------------------------------|--|

Statistical analysis description:

Percentage GLSM ratio is being presented. "Subjects in this analysis" states 84; however, only 42 unique participants were analyzed, each reported for Treatment B and Treatment A.

| | |
|---|------------------------------------|
| Comparison groups | Treatment B v Treatment A |
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[13] |
| Parameter estimate | Geometric least-squares mean ratio |
| Point estimate | 100.59 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 88.89 |
| upper limit | 113.83 |

Notes:

[13] - Statistical Comparison

| | |
|-----------------------------------|--|
| Statistical analysis title | GLSM ratio of GS-566500 (Treatment C vs B) |
|-----------------------------------|--|

Statistical analysis description:

Percentage GLSM ratio is being presented. "Subjects in this analysis" states 84; however, only 42 unique participants were analyzed, each reported for Treatment C and Treatment B.

| | |
|---|------------------------------------|
| Comparison groups | Treatment C v Treatment B |
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[14] |
| Parameter estimate | Geometric least-squares mean ratio |
| Point estimate | 163.23 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 144.62 |
| upper limit | 184.23 |

Notes:

[14] - Statistical Comparison

| | |
|-----------------------------------|--|
| Statistical analysis title | GLSM ratio of GS-331007 (Treatment B vs A) |
|-----------------------------------|--|

Statistical analysis description:

Percentage GLSM ratio is being presented. "Subjects in this analysis" states 84; however, only 42 unique participants were analyzed, each reported for Treatment B and Treatment A.

| | |
|---|------------------------------------|
| Comparison groups | Treatment A v Treatment B |
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[15] |
| Parameter estimate | Geometric least-squares mean ratio |
| Point estimate | 103.14 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 96.71 |
| upper limit | 110 |

Notes:

[15] - Statistical Comparison

| | |
|-----------------------------------|--|
| Statistical analysis title | GLSM ratio of GS-566500 (Treatment C vs B) |
|-----------------------------------|--|

Statistical analysis description:

Percentage GLSM ratio is being presented. "Subjects in this analysis" states 84; however, only 42 unique participants were analyzed, each reported for Treatment C and Treatment B.

| | |
|---|------------------------------------|
| Comparison groups | Treatment C v Treatment B |
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[16] |
| Parameter estimate | Geometric least-squares mean ratio |
| Point estimate | 103.12 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 97.61 |
| upper limit | 108.94 |

Notes:

[16] - Statistical Comparison

Primary: PK Parameter: AUClast of LDV

| | |
|-----------------|------------------------------|
| End point title | PK Parameter: AUClast of LDV |
|-----------------|------------------------------|

End point description:

AUClast is defined as the concentration of drug from time zero to the last observable concentration.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Predose, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 20, 24, 48, 72, 96, 120 and 144 hours postdose

| End point values | Treatment A | Treatment B | Treatment C | |
|--------------------------------------|----------------------|----------------------|----------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 39 ^[17] | 40 ^[18] | |
| Units: h*ng/mL | | | | |
| arithmetic mean (standard deviation) | 7362.3 (± 3557.92) | 6242.5 (± 2542.34) | 5149.6 (± 1349.23) | |

Notes:

[17] - 3 participants were excluded since their LDV predose plasma concentration was > 5% of C_{max}.

[18] - 2 participants were excluded since their LDV predose plasma concentration was > 5% of C_{max}.

Statistical analyses

| Statistical analysis title | GLSM ratio of LDV (Treatment B vs A) |
|----------------------------|--------------------------------------|
|----------------------------|--------------------------------------|

Statistical analysis description:

Percentage GLSM ratio is being presented. "Subjects in this analysis" states 81; however, only 42 unique participants were analyzed, each reported for Treatment B (N = 39) and Treatment A (N = 42).

| | |
|---|------------------------------------|
| Comparison groups | Treatment B v Treatment A |
| Number of subjects included in analysis | 81 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[19] |
| Parameter estimate | Geometric least-squares mean ratio |
| Point estimate | 87.76 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 77.94 |
| upper limit | 98.82 |

Notes:

[19] - Statistical Comparison

| Statistical analysis title | GLSM ratio of LDV (Treatment C vs B) |
|----------------------------|--------------------------------------|
|----------------------------|--------------------------------------|

Statistical analysis description:

Percentage GLSM ratio is being presented. "Subjects in this analysis" states 79; however, only 40 unique participants were analyzed, each reported for Treatment C (N = 40) and Treatment B (N = 39).

| | |
|---|------------------------------------|
| Comparison groups | Treatment C v Treatment B |
| Number of subjects included in analysis | 79 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[20] |
| Parameter estimate | Geometric least-squares mean ratio |
| Point estimate | 87.62 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 79.65 |
| upper limit | 96.39 |

Notes:

[20] - Statistical Comparison

Primary: PK Parameter: AUC_{inf} of SOF, GS-566500, and GS-331007

| | |
|-----------------|---|
| End point title | PK Parameter: AUC _{inf} of SOF, GS-566500, and GS-331007 |
|-----------------|---|

End point description:

AUCinf is defined as the concentration of drug extrapolated to infinite time.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Predose, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 20, 24, 48, 72, 96, 120 and 144 hours postdose

| End point values | Treatment A | Treatment B | Treatment C | |
|--------------------------------------|----------------------|----------------------|----------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 42 | 42 | |
| Units: h*ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| SOF | 1580.8 (± 634.96) | 1684.1 (± 733.08) | 2597.7 (± 853.35) | |
| GS-566500 | 1894.9 (± 584.25) | 2009.7 (± 663.88) | 2988.8 (± 558.28) | |
| GS-331007 | 11720.0 (± 3058.58) | 12095.0 (± 2947.17) | 12220.6 (± 2238.27) | |

Statistical analyses

| | |
|-----------------------------------|--------------------------------------|
| Statistical analysis title | GLSM ratio of SOF (Treatment B vs A) |
|-----------------------------------|--------------------------------------|

Statistical analysis description:

Percentage GLSM ratio is being presented. "Subjects in this analysis" states 84; however, only 42 unique participants were analyzed, each reported for Treatment B and Treatment A.

| | |
|---|------------------------------------|
| Comparison groups | Treatment B v Treatment A |
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[21] |
| Parameter estimate | Geometric least-squares mean ratio |
| Point estimate | 101.6 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 86.67 |
| upper limit | 119.1 |

Notes:

[21] - Statistical Comparison

| | |
|-----------------------------------|--------------------------------------|
| Statistical analysis title | GLSM ratio of SOF (Treatment C vs B) |
|-----------------------------------|--------------------------------------|

Statistical analysis description:

Percentage GLSM ratio is being presented. "Subjects in this analysis" states 84; however, only 42 unique participants were analyzed, each reported for Treatment C and Treatment B.

| | |
|-------------------|---------------------------|
| Comparison groups | Treatment C v Treatment B |
|-------------------|---------------------------|

| | |
|---|------------------------------------|
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[22] |
| Parameter estimate | Geometric least-squares mean ratio |
| Point estimate | 166.18 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 145.56 |
| upper limit | 189.71 |

Notes:

[22] - Statistical Comparison

| | |
|-----------------------------------|--|
| Statistical analysis title | GLSM ratio of GS-566500 (Treatment B vs A) |
|-----------------------------------|--|

Statistical analysis description:

Percentage GLSM ratio is being presented. "Subjects in this analysis" states 84; however, only 42 unique participants were analyzed, each reported for Treatment B and Treatment A.

| | |
|---|------------------------------------|
| Comparison groups | Treatment B v Treatment A |
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[23] |
| Parameter estimate | Geometric least-squares mean ratio |
| Point estimate | 101.37 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 90.17 |
| upper limit | 113.96 |

Notes:

[23] - Statistical Comparison

| | |
|-----------------------------------|--|
| Statistical analysis title | GLSM ratio of GS-566500 (Treatment C vs B) |
|-----------------------------------|--|

Statistical analysis description:

Percentage GLSM ratio is being presented. "Subjects in this analysis" states 84; however, only 42 unique participants were analyzed, each reported for Treatment C and Treatment B.

| | |
|---|------------------------------------|
| Comparison groups | Treatment C v Treatment B |
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[24] |
| Parameter estimate | Geometric least-squares mean ratio |
| Point estimate | 160.65 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 143.4 |
| upper limit | 179.99 |

Notes:

[24] - Statistical Comparison

| | |
|-----------------------------------|--|
| Statistical analysis title | GLSM ratio of GS-331007 (Treatment B vs A) |
|-----------------------------------|--|

Statistical analysis description:

Percentage GLSM ratio is being presented. "Subjects in this analysis" states 84; however, only 42 unique participants were analyzed, each reported for Treatment B and Treatment A.

| | |
|---|------------------------------------|
| Comparison groups | Treatment B v Treatment A |
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[25] |
| Parameter estimate | Geometric least-squares mean ratio |
| Point estimate | 103.64 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 98.48 |
| upper limit | 109.07 |

Notes:

[25] - Statistical Comparison

| | |
|-----------------------------------|--|
| Statistical analysis title | GLSM ratio of GS-331007 (Treatment C vs B) |
|-----------------------------------|--|

Statistical analysis description:

Percentage GLSM ratio is being presented. "Subjects in this analysis" states 84; however, only 42 unique participants were analyzed, each reported for Treatment C and Treatment B.

| | |
|---|------------------------------------|
| Comparison groups | Treatment C v Treatment B |
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[26] |
| Parameter estimate | Geometric least-squares mean ratio |
| Point estimate | 102.26 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 98.18 |
| upper limit | 106.52 |

Notes:

[26] - Statistical Comparison

Primary: PK Parameter: AUCinf of LDV

| | |
|-----------------|-----------------------------|
| End point title | PK Parameter: AUCinf of LDV |
|-----------------|-----------------------------|

End point description:

AUCinf is defined as the concentration of drug extrapolated to infinite time.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Predose, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 20, 24, 48, 72, 96, 120 and 144 hours postdose

| End point values | Treatment A | Treatment B | Treatment C | |
|--------------------------------------|----------------------|----------------------|----------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 39 ^[27] | 40 ^[28] | |
| Units: h*ng/mL | | | | |
| arithmetic mean (standard deviation) | 8467.5 (± 4605.87) | 7088.4 (± 3279.03) | 5748.3 (± 1669.51) | |

Notes:

[27] - 3 participants were excluded since their LDV predose plasma concentration was > 5% of C_{max}.

[28] - 2 participants were excluded since their LDV predose plasma concentration was > 5% of C_{max}.

Statistical analyses

| Statistical analysis title | GLSM ratio of LDV (Treatment B vs A) |
|----------------------------|--------------------------------------|
|----------------------------|--------------------------------------|

Statistical analysis description:

Percentage GLSM ratio is being presented. "Subjects in this analysis" states 81; however, only 42 unique participants were analyzed, each reported for Treatment B (N = 39) and Treatment A (N = 42).

| | |
|---|------------------------------------|
| Comparison groups | Treatment B v Treatment A |
| Number of subjects included in analysis | 81 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[29] |
| Parameter estimate | Geometric least-squares mean ratio |
| Point estimate | 88.36 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 78.43 |
| upper limit | 99.54 |

Notes:

[29] - Statistical Comparison

| Statistical analysis title | GLSM ratio of LDV (Treatment C vs B) |
|----------------------------|--------------------------------------|
|----------------------------|--------------------------------------|

Statistical analysis description:

Percentage GLSM ratio is being presented. "Subjects in this analysis" states 79; however, only 40 unique participants were analyzed, each reported for Treatment C (N = 40) and Treatment B (N = 39).

| | |
|---|------------------------------------|
| Comparison groups | Treatment C v Treatment B |
| Number of subjects included in analysis | 79 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[30] |
| Parameter estimate | Geometric least-squares mean ratio |
| Point estimate | 87.06 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 78.95 |
| upper limit | 96 |

Notes:

[30] - Statistical Comparison

Secondary: PK Parameter: T_{max} of SOF, GS-566500, and GS-331007

| | |
|-----------------|---|
| End point title | PK Parameter: T _{max} of SOF, GS-566500, and GS-331007 |
|-----------------|---|

End point description:

Tmax is defined as the time (observed time point) of Cmax.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Predose, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 20, 24, 48, 72, 96, 120 and 144 hours postdose

| End point values | Treatment A | Treatment B | Treatment C | |
|---------------------------------------|----------------------|----------------------|----------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 42 | 42 | |
| Units: hours | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| SOF | 0.51 (0.50 to 1.50) | 2.00 (1.00 to 2.50) | 1.50 (1.00 to 3.00) | |
| GS-566500 | 1.76 (1.00 to 2.00) | 2.50 (2.00 to 3.00) | 3.00 (2.50 to 4.00) | |
| GS-331007 | 3.00 (2.00 to 4.00) | 3.00 (2.50 to 3.50) | 4.50 (4.00 to 5.00) | |

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameter: Tmax of LDV

| | |
|-----------------|---------------------------|
| End point title | PK Parameter: Tmax of LDV |
|-----------------|---------------------------|

End point description:

Tmax is defined as the time (observed time point) of Cmax.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Predose, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 20, 24, 48, 72, 96, 120 and 144 hours postdose

| End point values | Treatment A | Treatment B | Treatment C | |
|---------------------------------------|----------------------|----------------------|----------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 39 ^[31] | 40 ^[32] | |
| Units: hours | | | | |
| median (inter-quartile range (Q1-Q3)) | 4.50 (4.50 to 4.55) | 4.50 (4.50 to 5.00) | 5.00 (4.50 to 6.00) | |

Notes:

[31] - 3 participants were excluded since their LDV predose plasma concentration was > 5% of Cmax.

[32] - 2 participants were excluded since their LDV predose plasma concentration was > 5% of Cmax.

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of Adverse Events

| | |
|-----------------|-----------------------------|
| End point title | Incidence of Adverse Events |
|-----------------|-----------------------------|

End point description:

The percentage of participants experiencing treatment-emergent adverse events was summarized.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From Baseline up to Day 21 plus 30 days

| End point values | Treatment A | Treatment B | Treatment C | |
|-----------------------------------|----------------------|----------------------|----------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 42 | 42 | |
| Units: percentage of participants | | | | |
| number (not applicable) | 9.5 | 9.5 | 14.3 | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

For Serious Adverse Events: From Screening until 30 days after last administration of study drug.

For Non-Serious Adverse Events: From Baseline until 30 days after last administration of study drug.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|----|
| Dictionary version | 19 |
|--------------------|----|

Reporting groups

| | |
|-----------------------|-------------|
| Reporting group title | Treatment A |
|-----------------------|-------------|

Reporting group description:

Single dose of LDV/SOF (90/400 mg tablet) under fasted condition (Treatment A)

| | |
|-----------------------|-------------|
| Reporting group title | Treatment B |
|-----------------------|-------------|

Reporting group description:

Single dose of LDV/SOF (8 x 11.25/50 mg oral granules) under fasted condition (Treatment B)

| | |
|-----------------------|-------------|
| Reporting group title | Treatment C |
|-----------------------|-------------|

Reporting group description:

Single dose of LDV/SOF (8 x 11.25/50 mg oral granules) under fed condition (Treatment C)

| Serious adverse events | Treatment A | Treatment B | Treatment C |
|---|----------------|----------------|----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 42 (0.00%) | 0 / 42 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |

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

| Non-serious adverse events | Treatment A | Treatment B | Treatment C |
|---|----------------|----------------|-----------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | 3 / 42 (7.14%) | 6 / 42 (14.29%) |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 3 / 42 (7.14%) | 3 / 42 (7.14%) |
| occurrences (all) | 1 | 3 | 4 |
| Gastrointestinal disorders | | | |
| Constipation | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 42 (0.00%) | 3 / 42 (7.14%) |
| occurrences (all) | 1 | 0 | 3 |

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