



Clinical trial results:

A Phase 2, Multicenter, Open-Label Study to Investigate the Safety and Efficacy of GS-7977 and Ribavirin for 24 Weeks in Subjects with Recurrent Chronic HCV Post Liver Transplant

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2012-002417-19 |
| Trial protocol | DE ES |
| Global end of trial date | 14 August 2014 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 20 February 2016 |
| First version publication date | 20 February 2016 |

Trial information

Trial identification

| | |
|-----------------------|----------------|
| Sponsor protocol code | GS-US-334-0126 |
|-----------------------|----------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01687270 |
| 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 Trial Information Desk, Gilead Sciences International Ltd, ClinicalTrialDisclosures@gilead.com |
| Scientific contact | Clinical Trial Information Desk, Gilead Sciences International Ltd, ClinicalTrialDisclosures@gilead.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 14 August 2014 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 14 August 2014 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

This was an open-label, single-arm study of sofosbuvir (SOF; GS-7977) and ribavirin (RBV) in adults who had a liver transplant which became re-infected with hepatitis C. The treatment period was 24 weeks with up to 48 weeks of follow up. The total time in this study lasted up to 72 weeks not including the screening visit.

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 | 26 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 | New Zealand: 3 |
| Country: Number of subjects enrolled | United States: 28 |
| Country: Number of subjects enrolled | Spain: 3 |
| Country: Number of subjects enrolled | France: 3 |
| Country: Number of subjects enrolled | Germany: 3 |
| Worldwide total number of subjects | 40 |
| EEA total number of subjects | 9 |

Notes:

Subjects enrolled per age group

| | |
|--|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 | 0 |

| | |
|--|----|
| wk | |
| 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) | 33 |
| From 65 to 84 years | 7 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at a total of 12 study sites in the United States, Europe, and New Zealand. The first participant was screened on 26 October 2012. The last participant observation occurred on 14 August 2014.

Pre-assignment

Screening details:

49 participants were screened.

Period 1

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

Arms

| | |
|------------------|---------|
| Arm title | SOF+RBV |
|------------------|---------|

Arm description:

Sofosbuvir (SOF) + ribavirin (RBV) for 24 weeks

| | |
|--|-----------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Sofosbuvir |
| Investigational medicinal product code | |
| Other name | Sovaldi®, GS-7977, PSI-7977 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Sofosbuvir (SOF) 400 mg tablet administered orally once daily

| | |
|--|-------------|
| Investigational medicinal product name | Ribavirin |
| Investigational medicinal product code | |
| Other name | Ribasphere® |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Ribavirin (RBV) 200-mg tablet(s) administered orally in a divided daily dose starting at 400 mg, subsequently adjusted (range: 200 to 1200 mg in a divided daily dose) based upon a number of factors including hemoglobin value, creatinine clearance, and weight.

| Number of subjects in period 1 | SOF+RBV |
|--------------------------------|---------|
| Started | 40 |
| Completed | 28 |
| Not completed | 12 |
| Lost to follow-up | 1 |
| Lack of efficacy | 11 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | Overall study |
|-----------------------|---------------|

Reporting group description:

SOF+RBV for 24 weeks

| Reporting group values | Overall study | Total | |
|-------------------------|---------------|-------|--|
| Number of subjects | 40 | 40 | |
| Age categorical | | | |
| Units: Subjects | | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 59 | | |
| standard deviation | ± 6.3 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 9 | 9 | |
| Male | 31 | 31 | |
| Ethnicity | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 1 | 1 | |
| Not Hispanic or Latino | 39 | 39 | |
| Unknown or Not Reported | 0 | 0 | |
| Race | | | |
| Units: Subjects | | | |
| White | 34 | 34 | |
| Black | 3 | 3 | |
| Asian | 2 | 2 | |
| Other | 1 | 1 | |
| HCV RNA Category | | | |
| Units: Subjects | | | |
| < 6 log10 IU/mL | 8 | 8 | |
| 6 to 7 log10 IU/mL | 20 | 20 | |
| > 7 log10 IU/mL | 12 | 12 | |
| Prior HCV Treatment | | | |
| Units: Subjects | | | |
| No | 5 | 5 | |
| Yes | 35 | 35 | |
| HCV Genotype | | | |
| Units: Subjects | | | |
| Genotype 1A | 22 | 22 | |
| Genotype 1B | 11 | 11 | |
| Genotype 3A | 5 | 5 | |
| Genotype 3B | 1 | 1 | |
| Genotype 4 | 1 | 1 | |
| IL28b Status | | | |

| | | | |
|---|---------|----|--|
| CC, CT, and TT alleles are different forms of the IL28b gene. | | | |
| Units: Subjects | | | |
| CC | 13 | 13 | |
| CT | 16 | 16 | |
| TT | 11 | 11 | |
| HCV RNA | | | |
| Units: log10 IU/mL | | | |
| arithmetic mean | 6.55 | | |
| standard deviation | ± 0.751 | - | |

End points

End points reporting groups

| | |
|---|---------|
| Reporting group title | SOF+RBV |
| Reporting group description: Sofosbuvir (SOF) + ribavirin (RBV) for 24 weeks | |

Primary: Percentage of Participants With Sustained Virologic Response 12 Weeks After Discontinuation of Therapy (SVR12)

| | |
|---|---|
| End point title | Percentage of Participants With Sustained Virologic Response 12 Weeks After Discontinuation of Therapy (SVR12) ^[1] |
| End point description: SVR12 was defined as HCV RNA < the lower limit of quantitation (LLOQ; ie, < 25 IU/mL) 12 weeks following the last dose of study drug. | |
| End point type | Primary |
| End point timeframe: Posttreatment Week 12 | |

Notes:

[1] - 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: No intergroup analysis was performed because the study was single-arm, and no analysis against a historic rate was performed because the study was not designed to demonstrate superiority or noninferiority.

| End point values | SOF+RBV | | | |
|-----------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 40 | | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 70 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Who Discontinue Study Drug Due to an Adverse Event

| | |
|---|--|
| End point title | Percentage of Participants Who Discontinue Study Drug Due to an Adverse Event ^[2] |
| End point description: | |
| End point type | Primary |
| End point timeframe: Baseline to Week 24 | |

Notes:

[2] - 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: No intergroup analysis was performed because the study was single-arm, and no analysis

against a historic rate was performed because the study was not designed to demonstrate superiority or noninferiority.

| | | | | |
|-----------------------------------|-----------------|--|--|--|
| End point values | SOF+RBV | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 40 | | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 5 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Sustained Virologic Response (SVR) at 4, 24, and 48 Weeks After Discontinuation of Therapy (SVR4, SVR24, and SVR48)

| | |
|--|---|
| End point title | Percentage of Participants With Sustained Virologic Response (SVR) at 4, 24, and 48 Weeks After Discontinuation of Therapy (SVR4, SVR24, and SVR48) |
| End point description: | |
| SVR4, SVR 24, and SVR 48 were defined as HCV RNA < LLOQ 4, 24, and 48 weeks following the last dose of study drug, respectively. | |
| End point type | Secondary |
| End point timeframe: | |
| Posttreatment Weeks 4, 24, and 48 | |

| | | | | |
|-----------------------------------|-----------------|--|--|--|
| End point values | SOF+RBV | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 40 | | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| SVR4 | 72.5 | | | |
| SVR24 | 70 | | | |
| SVR48 | 70 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With HCV RNA < LLOQ at Weeks 12 and 24

| | |
|------------------------|---|
| End point title | Percentage of Participants With HCV RNA < LLOQ at Weeks 12 and 24 |
| End point description: | |

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Weeks 12 and 24 | |

| End point values | SOF+RBV | | | |
|-----------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 40 | | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Week 12 (n = 40) | 100 | | | |
| Week 24 (n = 38) | 100 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: HCV RNA and Change From Baseline at Weeks 2, 4, and 8

| | |
|-----------------------------|---|
| End point title | HCV RNA and Change From Baseline at Weeks 2, 4, and 8 |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline; Weeks 2, 4, and 8 | |

| End point values | SOF+RBV | | | |
|---|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 40 | | | |
| Units: log10 IU/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 2 (n = 39) | 1.65 (± 0.37) | | | |
| Change from baseline at Week 2 (n = 39) | -4.89 (± 0.692) | | | |
| Week 4 (n = 40) | 1.38 (± 0) | | | |
| Change from baseline at Week 4 (n = 40) | -5.17 (± 0.751) | | | |
| Week 8 (n = 40) | 1.38 (± 0.005) | | | |
| Change from baseline at Week 8 (n = 40) | -5.17 (± 0.752) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Virologic Failure

| | |
|-----------------|---|
| End point title | Percentage of Participants With Virologic Failure |
|-----------------|---|

End point description:

Virologic failure was defined as on-treatment virologic failure or virologic relapse.

- On-treatment virologic failure: HCV RNA < LLOQ during treatment with subsequent detectable HCV RNA while continuing treatment

- Virologic relapse: HCV RNA < LLOQ at last observed on-treatment HCV RNA measurement and HCV RNA \geq LLOQ after stopping treatment (2 consecutive HCV RNA measurements or last available HCV RNA measurement)

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

End point timeframe:

Up to Posttreatment Week 24

| End point values | SOF+RBV | | | |
|-----------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 40 | | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| On-treatment virologic failure | 0 | | | |
| Virologic relapse | 30 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 24 weeks plus 30 days

Adverse event reporting additional description:

Safety Analysis set

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 17.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | SOF+RBV |
|-----------------------|---------|

Reporting group description:

SOF + RBV for 24 weeks

| Serious adverse events | SOF+RBV | | |
|--|-----------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 6 / 40 (15.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Injury, poisoning and procedural complications | | | |
| Compression fracture | | | |
| subjects affected / exposed | 1 / 40 (2.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 40 (5.00%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Ascites | | | |
| subjects affected / exposed | 1 / 40 (2.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |

| | | | |
|---|----------------|--|--|
| Jaundice | | | |
| subjects affected / exposed | 1 / 40 (2.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 1 / 40 (2.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hallucination | | | |
| subjects affected / exposed | 1 / 40 (2.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Haemarthrosis | | | |
| subjects affected / exposed | 1 / 40 (2.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 40 (2.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 40 (2.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| | | | |
|---|------------------|--|--|
| Non-serious adverse events | SOF+RBV | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 38 / 40 (95.00%) | | |
| General disorders and administration site conditions | | | |

| | | | |
|---|--|--|--|
| <p>Asthenia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>4 / 40 (10.00%)</p> <p>4</p> | | |
| <p>Fatigue</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>12 / 40 (30.00%)</p> <p>13</p> | | |
| <p>Oedema peripheral</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>3 / 40 (7.50%)</p> <p>3</p> | | |
| <p>Pyrexia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>2 / 40 (5.00%)</p> <p>3</p> | | |
| <p>Respiratory, thoracic and mediastinal disorders</p> <p>Cough</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dyspnoea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>7 / 40 (17.50%)</p> <p>7</p> <p>4 / 40 (10.00%)</p> <p>6</p> | | |
| <p>Psychiatric disorders</p> <p>Anxiety</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Depression</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Insomnia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Irritability</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>5 / 40 (12.50%)</p> <p>5</p> <p>3 / 40 (7.50%)</p> <p>3</p> <p>5 / 40 (12.50%)</p> <p>5</p> <p>4 / 40 (10.00%)</p> <p>5</p> | | |
| <p>Investigations</p> <p>Blood creatinine increased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>2 / 40 (5.00%)</p> <p>2</p> | | |

| | | | |
|---|---|--|--|
| Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all) Laceration subjects affected / exposed occurrences (all) | 2 / 40 (5.00%) 2 2 / 40 (5.00%) 2 | | |
| Cardiac disorders Palpitations subjects affected / exposed occurrences (all) | 3 / 40 (7.50%) 3 | | |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) | 3 / 40 (7.50%) 3 10 / 40 (25.00%) 11 | | |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Lymphopenia subjects affected / exposed occurrences (all) | 8 / 40 (20.00%) 8 2 / 40 (5.00%) 2 | | |
| Gastrointestinal disorders Abdominal distension subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Diarrhoea | 2 / 40 (5.00%) 2 2 / 40 (5.00%) 2 2 / 40 (5.00%) 2 | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 11 / 40 (27.50%) | | |
| occurrences (all) | 12 | | |
| Dyspepsia | | | |
| subjects affected / exposed | 2 / 40 (5.00%) | | |
| occurrences (all) | 2 | | |
| Nausea | | | |
| subjects affected / exposed | 8 / 40 (20.00%) | | |
| occurrences (all) | 9 | | |
| Oral lichen planus | | | |
| subjects affected / exposed | 3 / 40 (7.50%) | | |
| occurrences (all) | 3 | | |
| Vomiting | | | |
| subjects affected / exposed | 4 / 40 (10.00%) | | |
| occurrences (all) | 4 | | |
| Skin and subcutaneous tissue disorders | | | |
| Pruritus | | | |
| subjects affected / exposed | 3 / 40 (7.50%) | | |
| occurrences (all) | 3 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 9 / 40 (22.50%) | | |
| occurrences (all) | 12 | | |
| Back pain | | | |
| subjects affected / exposed | 2 / 40 (5.00%) | | |
| occurrences (all) | 2 | | |
| Muscle spasms | | | |
| subjects affected / exposed | 4 / 40 (10.00%) | | |
| occurrences (all) | 4 | | |
| Pain in extremity | | | |
| subjects affected / exposed | 3 / 40 (7.50%) | | |
| occurrences (all) | 3 | | |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 3 / 40 (7.50%) | | |
| occurrences (all) | 3 | | |
| Candida infection | | | |

| | | | |
|---|---------------------|--|--|
| subjects affected / exposed occurrences (all) | 2 / 40 (5.00%) 2 | | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 2 / 40 (5.00%) 2 | | |
| Sinusitis subjects affected / exposed occurrences (all) | 2 / 40 (5.00%) 2 | | |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 2 / 40 (5.00%) 2 | | |
| Metabolism and nutrition disorders | | | |
| Hypomagnesaemia subjects affected / exposed occurrences (all) | 2 / 40 (5.00%) 2 | | |
| Hypophosphataemia subjects affected / exposed occurrences (all) | 2 / 40 (5.00%) 2 | | |
| Increased appetite subjects affected / exposed occurrences (all) | 2 / 40 (5.00%) 2 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|----------------|---|
| 15 August 2012 | Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin criteria for discontinuation of study treatment (ie, stopping rules) were modified. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/25304641>