



Clinical trial results:

A Phase 3 Study Evaluating the Safety and Efficacy of Lambda/Ribavirin/Daclatasvir in Subjects with Chronic HCV Infection and Underlying Hemophilia Who are Treatment Naive or are Prior Relapsers to Peginterferon Alfa-2a/Ribavirin

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2012-003463-22 |
| Trial protocol | ES IT NL FR RO |
| Global end of trial date | 22 January 2015 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 23 April 2016 |
| First version publication date | 23 April 2016 |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | AI452-030 |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01741545 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Bristol Myers Squibb |
| Sponsor organisation address | Chaussee de la Hulpe 185, Brussels, Belgium, |
| Public contact | Bristol Myers Squibb Study Director, Bristol Myers Squibb, clinical.trials@bms.com |
| Scientific contact | Bristol Myers Squibb Study Director, Bristol Myers Squibb, clinical.trials@bms.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 | 22 January 2015 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 22 January 2015 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to evaluate the efficacy and safety of peginterferon lambda-1a (pegIFNλ-1a referred to as Lambda) in combination with the direct-acting antiviral agent daclatasvir (DCV) and ribavirin (RBV) in hemophilia subjects with genotype (GT)-1b, -2, -3, or -4 chronic hepatitis C virus (HCV) infection.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 25 March 2013 |
| 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 | Australia: 10 |
| Country: Number of subjects enrolled | France: 5 |
| Country: Number of subjects enrolled | Italy: 12 |
| Country: Number of subjects enrolled | Netherlands: 16 |
| Country: Number of subjects enrolled | Romania: 6 |
| Country: Number of subjects enrolled | Russian Federation: 12 |
| Country: Number of subjects enrolled | Spain: 8 |
| Country: Number of subjects enrolled | United States: 2 |
| Worldwide total number of subjects | 71 |
| EEA total number of subjects | 47 |

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) | 69 |
| From 65 to 84 years | 2 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 23 centres in 8 countries.

Pre-assignment

Screening details:

A total of 71 subjects were enrolled, of which 51 subjects were randomised and treated.

Period 1

| | |
|------------------------------|------------------|
| Period 1 title | Treatment period |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Blinding implementation details:

No blinding was performed as the study was open-label study.

Arms

| | |
|------------------------------|-----------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Cohort A (Treatment period) |

Arm description:

Subjects with HCV GT-2 or GT-3 infection (Cohort A) were to be treated with Lambda/Ribavirin/Daclatasvir. Subjects were administered daclatasvir 60 mg orally, once daily; pegIFN λ -1a 180 μ g subcutaneous injection, once weekly and ribavirin tablets, orally, twice daily (a total 800 mg per day) for 12 weeks treatment, 12 weeks and a maximum of 12 weeks, respectively.

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Daclatasvir |
| Investigational medicinal product code | BMS-790052 |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects were administered DCV 60 mg orally twice daily.

| | |
|--|--------------------|
| Investigational medicinal product name | Ribavirin |
| Investigational medicinal product code | |
| Other name | Ribasphere |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

2 ribavirin 200-mg tablets were administered twice daily for a total dose of 800 mg.

| | |
|--|--|
| Investigational medicinal product name | Peginterferon lambda-1a |
| Investigational medicinal product code | BMS-914143 |
| Other name | Lambda |
| Pharmaceutical forms | Solution for injection in pre-filled syringe |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Subjects were administered 180 μ g pegIFN α -2a subcutaneously.

| | |
|------------------|-----------------------------|
| Arm title | Cohort B (Treatment period) |
|------------------|-----------------------------|

Arm description:

Subjects with HCV GT-1b or GT-4 infection (Cohort B) were to be treated with Lambda/Ribavirin/Daclatasvir. Subjects were administered daclatasvir 60 mg orally, once daily, pegIFN λ -1a 180 μ g subcutaneous injection, once weekly and ribavirin tablets, twice daily, orally, based

on weight (subjects weighing <75 kg = 1000 mg and subjects weighing ≥75 kg = 1200 mg per day) for 12 weeks treatment, 24 weeks and a maximum of 24 weeks, respectively.

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Daclatasvir |
| Investigational medicinal product code | BMS-790052-05 |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects were administered DCV 60 mg orally twice daily.

| | |
|--|--------------------|
| Investigational medicinal product name | Ribavirin |
| Investigational medicinal product code | |
| Other name | Ribasphere |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects were administered ribavirin 200-mg tablets for a total daily dose stratified on body weight (<75kg=1000mg or ≥75kg=1200 mg).

| | |
|--|--|
| Investigational medicinal product name | Peginterferon lambda-1a |
| Investigational medicinal product code | BMS-914143 |
| Other name | Lambda |
| Pharmaceutical forms | Solution for injection in pre-filled syringe |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Subjects were administered 180 µg pegIFNα-2a subcutaneously.

| Number of subjects in period 1^[1] | Cohort A (Treatment period) | Cohort B (Treatment period) |
|---|-----------------------------|-----------------------------|
| Started | 12 | 39 |
| Completed | 11 | 35 |
| Not completed | 1 | 4 |
| Adverse event, non-fatal | 1 | 3 |
| Lack of efficacy | - | 1 |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The number of subjects reported in the baseline period are different from the worldwide number enrolled in the trial, as out of 71 subjects only 51 were randomised and received treatment in the study.

Period 2

| | |
|------------------------------|------------------|
| Period 2 title | Follow-up period |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Blinding implementation details:

No blinding was performed as the study was open-label study.

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|---|-----------------------------|
| Arm title | Cohort A (Follow-up period) |
| Arm description: | |
| Subjects with HCV GT-2 or GT-3 infection (Cohort A) were followed up for 24 weeks who received treatment with Lambda/RBV/DCV. Subjects were administered daclatasvir 60 mg orally, once daily; pegIFNλ-1a 180 µg subcutaneous injection, once weekly and ribavirin tablets, orally, twice daily (a total 800 mg per day) for 12 weeks treatment, 12 weeks and a maximum of 12 weeks, respectively. | |
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |
| Arm title | Cohort B (Follow-up period) |
| Arm description: | |
| Subjects with HCV GT-1b or GT-4 infection (Cohort B) were followed up for 24 weeks who received treatment with Lambda/RBV/DCV. Subjects were administered daclatasvir 60 mg orally, once daily, pegIFNλ-1a 180 µg subcutaneous injection, once weekly and ribavirin tablets, twice daily, orally, based on weight (subjects weighing <75 kg = 1000 mg and subjects weighing ≥75 kg = 1200 mg per day) for 12 weeks treatment, 24 weeks and a maximum of 24 weeks, respectively. | |
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |

| Number of subjects in period 2 | Cohort A (Follow-up period) | Cohort B (Follow-up period) |
|---------------------------------------|-----------------------------|-----------------------------|
| Started | 11 | 35 |
| Completed | 11 | 37 |
| Not completed | 1 | 2 |
| Consent withdrawn by subject | 1 | 1 |
| Other reason | - | 1 |
| Joined | 1 | 4 |
| Rejoined for follow-up | 1 | 4 |

Baseline characteristics

Reporting groups

| | |
|--|-----------------------------|
| Reporting group title | Cohort A (Treatment period) |
| Reporting group description: | |
| Subjects with HCV GT-2 or GT-3 infection (Cohort A) were to be treated with Lambda/Ribavirin/Daclatasvir. Subjects were administered daclatasvir 60 mg orally, once daily; pegIFN λ -1a 180 μ g subcutaneous injection, once weekly and ribavirin tablets, orally, twice daily (a total 800 mg per day) for 12 weeks treatment, 12 weeks and a maximum of 12 weeks, respectively. | |
| Reporting group title | Cohort B (Treatment period) |
| Reporting group description: | |
| Subjects with HCV GT-1b or GT-4 infection (Cohort B) were to be treated with Lambda/Ribavirin/Daclatasvir. Subjects were administered daclatasvir 60 mg orally, once daily, pegIFN λ -1a 180 μ g subcutaneous injection, once weekly and ribavirin tablets, twice daily, orally, based on weight (subjects weighing <75 kg = 1000 mg and subjects weighing \geq 75 kg = 1200 mg per day) for 12 weeks treatment, 24 weeks and a maximum of 24 weeks, respectively. | |

| Reporting group values | Cohort A (Treatment period) | Cohort B (Treatment period) | Total |
|------------------------|-----------------------------|-----------------------------|-------|
| Number of subjects | 12 | 39 | 51 |
| Age categorical | | | |
| Units: Subjects | | | |
| 21 - <65 years | 12 | 38 | 50 |
| \geq 65 years | 0 | 1 | 1 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 42.8 | 45.2 | - |
| standard deviation | \pm 9.94 | \pm 12.04 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Male | 12 | 39 | 51 |
| HCV Genotype | | | |
| Units: Subjects | | | |
| Genotype 1A | 0 | 0 | 0 |
| Genotype 1B | 0 | 39 | 39 |
| Genotype 2 | 2 | 0 | 2 |
| Genotype 3 | 10 | 0 | 10 |
| Genotype 4 | 0 | 0 | 0 |

End points

End points reporting groups

| | |
|-----------------------|-----------------------------|
| Reporting group title | Cohort A (Treatment period) |
|-----------------------|-----------------------------|

Reporting group description:

Subjects with HCV GT-2 or GT-3 infection (Cohort A) were to be treated with Lambda/Ribavirin/Daclatasvir. Subjects were administered daclatasvir 60 mg orally, once daily; pegIFN λ -1a 180 μ g subcutaneous injection, once weekly and ribavirin tablets, orally, twice daily (a total 800 mg per day) for 12 weeks treatment, 12 weeks and a maximum of 12 weeks, respectively.

| | |
|-----------------------|-----------------------------|
| Reporting group title | Cohort B (Treatment period) |
|-----------------------|-----------------------------|

Reporting group description:

Subjects with HCV GT-1b or GT-4 infection (Cohort B) were to be treated with Lambda/Ribavirin/Daclatasvir. Subjects were administered daclatasvir 60 mg orally, once daily, pegIFN λ -1a 180 μ g subcutaneous injection, once weekly and ribavirin tablets, twice daily, orally, based on weight (subjects weighing <75 kg = 1000 mg and subjects weighing \geq 75 kg = 1200 mg per day) for 12 weeks treatment, 24 weeks and a maximum of 24 weeks, respectively.

| | |
|-----------------------|-----------------------------|
| Reporting group title | Cohort A (Follow-up period) |
|-----------------------|-----------------------------|

Reporting group description:

Subjects with HCV GT-2 or GT-3 infection (Cohort A) were followed up for 24 weeks who received treatment with Lambda/RBV/DCV. Subjects were administered daclatasvir 60 mg orally, once daily; pegIFN λ -1a 180 μ g subcutaneous injection, once weekly and ribavirin tablets, orally, twice daily (a total 800 mg per day) for 12 weeks treatment, 12 weeks and a maximum of 12 weeks, respectively.

| | |
|-----------------------|-----------------------------|
| Reporting group title | Cohort B (Follow-up period) |
|-----------------------|-----------------------------|

Reporting group description:

Subjects with HCV GT-1b or GT-4 infection (Cohort B) were followed up for 24 weeks who received treatment with Lambda/RBV/DCV. Subjects were administered daclatasvir 60 mg orally, once daily, pegIFN λ -1a 180 μ g subcutaneous injection, once weekly and ribavirin tablets, twice daily, orally, based on weight (subjects weighing <75 kg = 1000 mg and subjects weighing \geq 75 kg = 1200 mg per day) for 12 weeks treatment, 24 weeks and a maximum of 24 weeks, respectively.

| | |
|----------------------------|--|
| Subject analysis set title | Cohort A (Treatment and Follow-up periods) |
|----------------------------|--|

| | |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

Subjects with HCV GT-2 or GT-3 infection (Cohort A) were followed up for 24 weeks who received treatment with Lambda/RBV/DCV. During treatment period subjects received daclatasvir 60 mg orally, once daily; pegIFN λ -1a 180 μ g subcutaneous injection, once weekly and ribavirin tablets, orally, twice daily (a total 800 mg per day) for 12 weeks treatment, 12 weeks and a maximum of 12 weeks, respectively.

| | |
|----------------------------|--|
| Subject analysis set title | Cohort B (Treatment and Follow-up periods) |
|----------------------------|--|

| | |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

Subjects with HCV GT-1b or GT-4 infection (Cohort B) were followed up for 24 weeks who received treatment with Lambda/RBV/DCV. During treatment period subjects received daclatasvir 60 mg orally, once daily, pegIFN λ -1a 180 μ g subcutaneous injection, once weekly and ribavirin tablets, twice daily, orally, based on weight (subjects weighing <75 kg = 1000 mg and subjects weighing \geq 75 kg = 1200 mg per day) for 12 weeks treatment, 24 weeks and a maximum of 24 weeks, respectively.

Primary: Percentage of Subjects Who Achieve Sustained Virologic Response (SVR12) at Follow-Up Week 12

| | |
|-----------------|---|
| End point title | Percentage of Subjects Who Achieve Sustained Virologic Response (SVR12) at Follow-Up Week 12 ^[1] |
|-----------------|---|

End point description:

SVR12 was defined as hepatitis C virus (HCV) RNA less than the lower limit of quantitation, target detected or target not detected at follow-up Week 12. The analysis was performed in modified intent to treat population defined as subjects meeting the response criteria over all treated subjects.

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

End point timeframe:

Follow-up 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: Only descriptive summary statistics was planned for this outcome measure.

| End point values | Cohort A (Follow-up period) | Cohort B (Follow-up period) | | |
|----------------------------------|-----------------------------------|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 12 | 39 | | |
| Units: Percentage of subjects | | | | |
| number (confidence interval 95%) | 91.7 (61.5 to 99.8) | 89.7 (75.8 to 97.1) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Rapid Virologic Response (RVR)

| | |
|-----------------|--|
| End point title | Percentage of Subjects With Rapid Virologic Response (RVR) |
|-----------------|--|

End point description:

RVR was defined as hepatitis C virus (HCV) RNA less than the lower limit of quantitation, target not detected at Week 4. The analysis was performed in modified intent to treat population defined as subjects meeting the response criteria over all treated subjects.

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

End point timeframe:

Week 4

| End point values | Cohort A (Treatment period) | Cohort B (Treatment period) | | |
|----------------------------------|-----------------------------------|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 12 | 39 | | |
| Units: Percentage of subjects | | | | |
| number (confidence interval 95%) | 91.7 (61.5 to 99.8) | 76.9 (60.7 to 88.9) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects With Complete Early Virologic Response (cEVR)

| | |
|-----------------|--|
| End point title | Percentage of subjects With Complete Early Virologic Response (cEVR) |
|-----------------|--|

End point description:

cEVR was defined as hepatitis C virus (HCV) RNA less than the lower limit of quantitation, target not detected at Week 12. The analysis was performed in modified intent to treat population defined as

subjects meeting the response criteria over all treated subjects.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Week 12 | |

| End point values | Cohort A (Treatment period) | Cohort B (Treatment period) | | |
|----------------------------------|-----------------------------------|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 12 | 39 | | |
| Units: Percentage of subjects | | | | |
| number (confidence interval 95%) | 91.7 (61.5 to 99.8) | 92.3 (79.1 to 98.4) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With End of the Treatment Response (EOTR)

| | |
|-----------------|--|
| End point title | Percentage of Subjects With End of the Treatment Response (EOTR) |
|-----------------|--|

End point description:

EOTR was defined as hepatitis C virus (HCV) RNA less than the lower limit of quantitation, target not detected at end of treatment. The analysis was performed in modified intent to treat population defined as subjects meeting the response criteria over all treated subjects.

| | |
|--------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| End of the treatment (Week 24) | |

| End point values | Cohort A (Treatment period) | Cohort B (Treatment period) | | |
|----------------------------------|-----------------------------------|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 12 | 39 | | |
| Units: Percentage of subjects | | | | |
| number (confidence interval 95%) | 100 (73.5 to 100) | 100 (91 to 100) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Sustained Virologic Response at Follow-Up Week 24 (SVR24)

| | |
|---|---|
| End point title | Percentage of Subjects With Sustained Virologic Response at Follow-Up Week 24 (SVR24) |
| End point description: SVR24 was defined as hepatitis C virus (HCV) RNA less than the lower limit of quantitation, target detected or target not detected at follow-up week 24. The analysis was performed in modified intent to treat population defined as subjects meeting the response criteria over all treated subjects. | |
| End point type | Secondary |
| End point timeframe: Follow-up Week 24 Follow-up | |

| End point values | Cohort A (Follow-up period) | Cohort B (Follow-up period) | | |
|----------------------------------|--------------------------------|--------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 12 | 39 | | |
| Units: Percentage of subjects | | | | |
| number (confidence interval 95%) | 66.7 (34.9 to 90.1) | 30.8 (17 to 47.6) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Treatment-Emergent Cytopenic Abnormalities On-Treatment

| | |
|--|---|
| End point title | Percentage of Subjects With Treatment-Emergent Cytopenic Abnormalities On-Treatment |
| End point description: Cytopenic abnormalities were defined as anemia as defined by Hb <10 g/dL, and/or neutropenia as defined by ANC <750 mm ³ , and/or thrombocytopenia as defined by platelets <50,000 mm ³ . The analysis was performed in modified intent to treat population defined as subjects meeting the response criteria over all treated subjects. | |
| End point type | Secondary |
| End point timeframe: After Day 1 to end of treatment | |

| End point values | Cohort A (Treatment period) | Cohort B (Treatment period) | | |
|----------------------------------|--------------------------------|--------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 12 | 39 | | |
| Units: Percentage of subjects | | | | |
| number (confidence interval 95%) | 0 (0 to 26.5) | 0 (0 to 9) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Flu-Like Symptoms and Musculoskeletal Symptoms On-Treatment

| | |
|-----------------|---|
| End point title | Percentage of Subjects With Flu-Like Symptoms and Musculoskeletal Symptoms On-Treatment |
|-----------------|---|

End point description:

Flu-like symptoms were defined as pyrexia or chills or pain. Musculoskeletal symptoms were defined as arthralgia or myalgia or back pain. The analysis was performed in modified intent to treat population defined as subjects meeting the response criteria over all treated subjects.

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

End point timeframe:

Day 1 to end of treatment

| End point values | Cohort A (Treatment period) | Cohort B (Treatment period) | | |
|----------------------------------|-----------------------------------|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 12 | 39 | | |
| Units: Percentage of subjects | | | | |
| number (confidence interval 95%) | | | | |
| Flu-like symptoms | 8.3 (0.2 to 38.5) | 12.8 (4.3 to 27.4) | | |
| Musculoskeletal symptoms | 0 (0 to 26.5) | 15.4 (5.9 to 30.5) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Adverse Events (AEs), Serious Adverse Events (SAEs), AEs Leading to Discontinuation, Dose Reductions, And Who Died

| | |
|-----------------|--|
| End point title | Percentage of Subjects With Adverse Events (AEs), Serious Adverse Events (SAEs), AEs Leading to Discontinuation, Dose Reductions, And Who Died |
|-----------------|--|

End point description:

AE=any new untoward medical event or worsening of a preexisting medical condition that does not necessarily have a causal relationship with this treatment. SAE=any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalization or causes prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, results in development of drug dependency or drug abuse, is an important medical event. Treatment-related SAE=possibly, probably, or certainly related to study drug. The analysis was performed on all treated subjects.

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

End point timeframe:

From Day 1 to end of follow-up (maximum of 60 weeks for Cohort A and 72 weeks for Cohort B)

| End point values | Cohort A (Treatment and Follow-up periods) | Cohort B (Treatment and Follow-up periods) | | |
|-------------------------------|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 12 | 39 | | |
| Units: Subjects | | | | |
| AEs on treatment | 10 | 38 | | |
| SAEs | 0 | 4 | | |
| Death | 0 | 0 | | |
| AE leading to discontinuation | 1 | 3 | | |
| Dose reduction - Lambda | 0 | 1 | | |
| Dose reduction - RBV | 0 | 2 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment Emergent Grade 3 to 4 Laboratory Abnormalities

| | |
|--|--|
| End point title | Number of Subjects With Treatment Emergent Grade 3 to 4 Laboratory Abnormalities |
| End point description: | |
| Laboratory abnormalities were determined and graded using the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 1.0. International Normalized Ratio (INR): >2.0*Upper limit of normal (ULN); Alanine aminotransferase (ALT) : >5*ULN; Aspartate aminotransferase (AST): >5*ULN; Prothrombin Time (PT): >1.50*ULN; Bilirubin (Total): >2.5*ULN; Triglycerides (fasting): >750 mg/dL. The analysis was performed on all treated subjects. | |
| End point type | Secondary |
| End point timeframe: | |
| After Day 1 to end of treatment | |

| End point values | Cohort A (Treatment period) | Cohort B (Treatment period) | | |
|-----------------------------|-----------------------------------|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 12 | 39 | | |
| Units: Subjects | | | | |
| INR | 0 | 1 | | |
| ALT | 2 | 1 | | |
| AST | 0 | 2 | | |
| PT | 0 | 1 | | |
| Bilirubin | 2 | 7 | | |
| Triglycerides | 0 | 1 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

After Day 1 to end of treatment

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 17.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-----------------------------|
| Reporting group title | Cohort A (Treatment period) |
|-----------------------|-----------------------------|

Reporting group description:

Subjects with HCV GT-2 or GT-3 infection (Cohort A) were to be treated with Lambda/RBV/DCV. Subjects were administered with once daily DCV 60 mg orally, once weekly pegIFN λ -1a 180 μ g SC injection and twice daily RBV a total 800 mg per day for 12 weeks treatment, 12 weeks and a maximum of 12 weeks, respectively.

| | |
|-----------------------|-----------------------------|
| Reporting group title | Cohort B (Treatment period) |
|-----------------------|-----------------------------|

Reporting group description:

Subjects with HCV GT-1b or GT-4 infection (Cohort B) were to be treated with Lambda/RBV/DCV. Subjects were administered with once daily DCV 60 mg orally, once weekly pegIFN λ -1a 180 μ g SC injection and twice daily RBV based on weight (subjects weighing <75 kg = 1000 mg and subjects weighing \geq 75 kg = 1200 mg per day) for 12 weeks treatment, 24 weeks and a maximum of 24 weeks, respectively.

| Serious adverse events | Cohort A (Treatment period) | Cohort B (Treatment period) | |
|---|-----------------------------|-----------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 2 / 39 (5.13%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |
| Hepatobiliary disorders | | | |
| Hepatitis acute | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 39 (2.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Jaundice | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 39 (2.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Cohort A (Treatment period) | Cohort B (Treatment period) | |
|--|-----------------------------|-----------------------------|--|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 10 / 12 (83.33%) | 36 / 39 (92.31%) | |
| Vascular disorders | | | |
| Haematoma | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 3 / 39 (7.69%) | |
| occurrences (all) | 0 | 4 | |
| Haemorrhage | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 2 / 39 (5.13%) | |
| occurrences (all) | 0 | 3 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 12 / 39 (30.77%) | |
| occurrences (all) | 0 | 13 | |
| Fatigue | | | |
| subjects affected / exposed | 3 / 12 (25.00%) | 9 / 39 (23.08%) | |
| occurrences (all) | 3 | 9 | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 5 / 39 (12.82%) | |
| occurrences (all) | 1 | 6 | |
| Influenza like illness | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 39 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pain | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 39 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 3 / 39 (7.69%) | |
| occurrences (all) | 0 | 4 | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 39 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Psychiatric disorders | | | |
| Insomnia | | | |

| | | | |
|---|----------------------|------------------------|--|
| subjects affected / exposed occurrences (all) | 3 / 12 (25.00%) 3 | 13 / 39 (33.33%) 16 | |
| Sleep disorder subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 5 / 39 (12.82%) 5 | |
| Affect lability subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 2 / 39 (5.13%) 2 | |
| Anger subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 2 / 39 (5.13%) 2 | |
| Anxiety subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 2 / 39 (5.13%) 2 | |
| Irritability subjects affected / exposed occurrences (all) | 2 / 12 (16.67%) 2 | 2 / 39 (5.13%) 2 | |
| Depression subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 39 (0.00%) 0 | |
| Initial insomnia subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 39 (0.00%) 0 | |
| Investigations Blood bilirubin increased subjects affected / exposed occurrences (all) | 2 / 12 (16.67%) 2 | 2 / 39 (5.13%) 2 | |
| Weight decreased subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 2 / 39 (5.13%) 2 | |
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 2 | 1 / 39 (2.56%) 1 | |
| Lipase increased subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 1 / 39 (2.56%) 3 | |

| | | | |
|---|----------------------|-----------------------|--|
| Blood bicarbonate decreased subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 39 (0.00%) 0 | |
| Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 39 (0.00%) 0 | |
| Nervous system disorders | | | |
| Headache subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 7 / 39 (17.95%) 14 | |
| Dizziness subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 3 / 39 (7.69%) 3 | |
| Disturbance in attention subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 2 / 39 (5.13%) 2 | |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 39 (0.00%) 0 | |
| Gastrointestinal disorders | | | |
| Nausea subjects affected / exposed occurrences (all) | 2 / 12 (16.67%) 3 | 8 / 39 (20.51%) 9 | |
| Diarrhoea subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 6 / 39 (15.38%) 6 | |
| Abdominal pain subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 3 / 39 (7.69%) 3 | |
| Dry mouth subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 3 / 39 (7.69%) 3 | |
| Dyspepsia subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 2 / 39 (5.13%) 2 | |

| | | | |
|--|----------------------|----------------------|--|
| Rectal haemorrhage subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 2 / 39 (5.13%) 2 | |
| Vomiting subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 2 / 39 (5.13%) 2 | |
| Skin and subcutaneous tissue disorders | | | |
| Pruritus subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 7 / 39 (17.95%) 7 | |
| Dry skin subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 4 / 39 (10.26%) 5 | |
| Rash subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 1 / 39 (2.56%) 1 | |
| Renal and urinary disorders | | | |
| Chromaturia subjects affected / exposed occurrences (all) | 2 / 12 (16.67%) 2 | 4 / 39 (10.26%) 4 | |
| Endocrine disorders | | | |
| Hypothyroidism subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 39 (0.00%) 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 4 / 39 (10.26%) 4 | |
| Haemarthrosis subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 2 / 39 (5.13%) 2 | |
| Myalgia subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 2 / 39 (5.13%) 2 | |
| Metabolism and nutrition disorders | | | |

| | | | |
|--|----------------------|----------------------|--|
| Decreased appetite subjects affected / exposed occurrences (all) | 2 / 12 (16.67%) 2 | 5 / 39 (12.82%) 5 | |
|--|----------------------|----------------------|--|

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 12 November 2012 | Removed GT-1a subjects from being eligible to participate in the trial. |
| 19 July 2013 | Updated to exclude cirrhotic subjects who have evidence of preexisting portal hypertension. |
| 24 October 2013 | Updated to include severe hemophiliacs, change in Medical Monitor. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported