



## Clinical trial results:

### A Phase 2, Open-label Study to Investigate the Efficacy and Safety of the Combination of Simeprevir and Daclatasvir in Chronic Hepatitis C Genotype 1b-infected Subjects

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2014-003413-28 |
| Trial protocol           | HU GB DE BE ES |
| Global end of trial date | 11 April 2016  |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 01 February 2017 |
| First version publication date | 01 February 2017 |

#### Trial information

##### Trial identification

|                       |               |
|-----------------------|---------------|
| Sponsor protocol code | TMC435HPC2019 |
|-----------------------|---------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02268864 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Janssen-Cilag International NV   |
| Sponsor organisation address | Lammerdries-Oost 55, Olen, Belgium, 2250   |
| Public contact               | Clinical Registry Group, Janssen-Cilag International NV,<br>clinicaltrialsEU@its.jnj.com |
| Scientific contact           | Clinical Registry Group, Janssen-Cilag International NV,<br>clinicaltrialsEU@its.jnj.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                       | 11 April 2016 |
| Is this the analysis of the primary completion data? | No            |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 11 April 2016 |
| Was the trial ended prematurely?                     | No            |

Notes:

## General information about the trial

Main objective of the trial:

The main objective of this study was to determine the efficacy of a treatment regimen of simeprevir in combination with daclatasvir, as measured by sustained virologic response (SVR) at 12 weeks after actual end of treatment (EOT) (SVR12), in treatment-naïve, chronic hepatitis C virus (HCV) genotype 1b-infected subjects who had advanced fibrosis or compensated cirrhosis (corresponding to METAVIR F3/F4).

Protection of trial subjects:

Safety evaluations included the monitoring of adverse events (AEs), clinical laboratory test results, vital sign measurements, and physical examinations. An electrocardiogram (ECG) was performed during screening.

Background therapy: -

Evidence for comparator: -

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 14 January 2015 |
| 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 | Belgium: 12       |
| Country: Number of subjects enrolled | Germany: 20       |
| Country: Number of subjects enrolled | Spain: 20         |
| Country: Number of subjects enrolled | France: 25        |
| Country: Number of subjects enrolled | United Kingdom: 1 |
| Country: Number of subjects enrolled | Hungary: 12       |
| Country: Number of subjects enrolled | Italy: 16         |
| Worldwide total number of subjects   | 106               |
| EEA total number of subjects         | 106               |

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)                     | 75 |
| From 65 to 84 years                      | 31 |
| 85 years and over                        | 0  |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

In total, 197 subjects were screened. Of these, 106 subjects (53.8%) were treated (Cohort 1 exclusively). In Cohort 1, 21.3% of the subjects (42/197) were screening failures, and 1 subject was enrolled but not treated.

### Period 1

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

### Arms

|                              |                          |
|------------------------------|--------------------------|
| Are arms mutually exclusive? | Yes                      |
| <b>Arm title</b>             | 12 Weeks Prior Amendment |

Arm description:

Simeprevir 150 milligram (mg) once daily as an oral capsule in combination with Daclatasvir 60 mg once daily as an oral tablet for subjects who completed the 12-week treatment before Amendment 3 of the protocol was implemented.

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Simeprevir   |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Capsule      |
| Routes of administration               | Oral use     |

Dosage and administration details:

Simeprevir 150 milligram (mg) once daily as an oral capsule for subjects who completed the 12-week treatment before Amendment 3 of the protocol was implemented.

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

Dosage and administration details:

Daclatasvir 60 mg once daily as an oral tablet for subjects who completed the 12-week treatment before Amendment 3 of the protocol was implemented.

|                  |                         |
|------------------|-------------------------|
| <b>Arm title</b> | 12 Weeks Post Amendment |
|------------------|-------------------------|

Arm description:

Simeprevir 150 mg once daily as an oral capsule in combination with Daclatasvir 60 mg once daily as an oral tablet for subjects who opted for a 12-week treatment period after amendment.

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Simeprevir   |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Capsule      |
| Routes of administration               | Oral use     |

Dosage and administration details:

Simeprevir 150 mg once daily as an oral capsule for subjects who opted for a 12-week treatment period after amendment.

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

Dosage and administration details:

Daclatasvir 60 mg once daily as an oral tablet for subjects who opted for a 12-week treatment period after amendment.

|                  |                    |
|------------------|--------------------|
| <b>Arm title</b> | 24 Weeks Extension |
|------------------|--------------------|

Arm description:

Simeprevir 150 mg once daily as an oral capsule in combination with Daclatasvir 60 mg once daily as an oral tablet for subjects who opted for an extended 24-week treatment after amendment.

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Simeprevir   |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Capsule      |
| Routes of administration               | Oral use     |

Dosage and administration details:

Simeprevir 150 mg once daily as an oral capsule for subjects who opted for an extended 24-week treatment after amendment.

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

Dosage and administration details:

Daclatasvir 60 mg once daily as an oral tablet for subjects who opted for an extended 24-week treatment after amendment.

| <b>Number of subjects in period 1</b> | 12 Weeks Prior Amendment | 12 Weeks Post Amendment | 24 Weeks Extension |
|---------------------------------------|--------------------------|-------------------------|--------------------|
| Started                               | 17                       | 25                      | 64                 |
| Completed                             | 15                       | 24                      | 64                 |
| Not completed                         | 2                        | 1                       | 0                  |
| Adverse event, serious fatal          | -                        | 1                       | -                  |
| Consent withdrawn by subject          | 2                        | -                       | -                  |

## Baseline characteristics

### Reporting groups

|   |                          |
|---|--------------------------|
| Reporting group title   | 12 Weeks Prior Amendment |
| Reporting group description:<br>Simeprevir 150 milligram (mg) once daily as an oral capsule in combination with Daclatasvir 60 mg once daily as an oral tablet for subjects who completed the 12-week treatment before Amendment 3 of the protocol was implemented. |                          |
| Reporting group title   | 12 Weeks Post Amendment  |
| Reporting group description:<br>Simeprevir 150 mg once daily as an oral capsule in combination with Daclatasvir 60 mg once daily as an oral tablet for subjects who opted for a 12-week treatment period after amendment.   |                          |
| Reporting group title   | 24 Weeks Extension       |
| Reporting group description:<br>Simeprevir 150 mg once daily as an oral capsule in combination with Daclatasvir 60 mg once daily as an oral tablet for subjects who opted for an extended 24-week treatment after amendment.  |                          |

| Reporting group values                      | 12 Weeks Prior Amendment | 12 Weeks Post Amendment | 24 Weeks Extension |
|---|--------------------------|-------------------------|--------------------|
| Number of subjects                          | 17                       | 25                      | 64                 |
| Title for AgeCategorical<br>Units: subjects |                          |                         |                    |
| Children (2-11 years)                       | 0                        | 0                       | 0                  |
| Adolescents (12-17 years)                   | 0                        | 0                       | 0                  |
| Adults (18-64 years)                        | 12                       | 15                      | 48                 |
| From 65 to 84 years                         | 5                        | 10                      | 16                 |
| 85 years and over                           | 0                        | 0                       | 0                  |
| Title for AgeContinuous<br>Units: years     |                          |                         |                    |
| median                                      | 53                       | 64                      | 59                 |
| full range (min-max)                        | 21 to 82                 | 25 to 83                | 26 to 83           |
| Title for Gender<br>Units: subjects         |                          |                         |                    |
| Female                                      | 5                        | 11                      | 27                 |
| Male  | 12                       | 14                      | 37                 |

| Reporting group values                      | Total |  |  |
|---|-------|--|--|
| Number of subjects                          | 106   |  |  |
| Title for AgeCategorical<br>Units: subjects |       |  |  |
| Children (2-11 years)                       | 0     |  |  |
| Adolescents (12-17 years)                   | 0     |  |  |
| Adults (18-64 years)                        | 75    |  |  |
| From 65 to 84 years                         | 31    |  |  |
| 85 years and over                           | 0     |  |  |
| Title for AgeContinuous<br>Units: years     |       |  |  |
| median                                      |       |  |  |
| full range (min-max)                        | -     |  |  |

|                  |    |  |  |
|------------------|----|--|--|
| Title for Gender |    |  |  |
| Units: subjects  |    |  |  |
| Female           | 43 |  |  |
| Male             | 63 |  |  |

## End points

### End points reporting groups

|   |                          |
|---|--------------------------|
| Reporting group title   | 12 Weeks Prior Amendment |
| Reporting group description:<br>Simeprevir 150 milligram (mg) once daily as an oral capsule in combination with Daclatasvir 60 mg once daily as an oral tablet for subjects who completed the 12-week treatment before Amendment 3 of the protocol was implemented. |                          |
| Reporting group title   | 12 Weeks Post Amendment  |
| Reporting group description:<br>Simeprevir 150 mg once daily as an oral capsule in combination with Daclatasvir 60 mg once daily as an oral tablet for subjects who opted for a 12-week treatment period after amendment.   |                          |
| Reporting group title   | 24 Weeks Extension       |
| Reporting group description:<br>Simeprevir 150 mg once daily as an oral capsule in combination with Daclatasvir 60 mg once daily as an oral tablet for subjects who opted for an extended 24-week treatment after amendment.  |                          |

### Primary: Percentage of Subjects With Sustained Virologic Response 12 Weeks After end of Study Drug Treatment (SVR12)

|  |  |
|--|--|
| End point title  | Percentage of Subjects With Sustained Virologic Response 12 Weeks After end of Study Drug Treatment (SVR12) <sup>[1]</sup> |
| End point description:<br>Subjects were considered to have reached SVR12, if 12 weeks after the actual end of treatment (EOT), hepatitis C virus (HCV) ribonucleic acid (RNA) was less than lower limit of quantification (<LLOQ) (detectable or undetectable). The intent-to-treat (ITT) analysis set is defined as all subjects who received at least one dose of simeprevir or daclatasvir. |  |
| End point type   | Primary  |
| End point timeframe:<br>At 12 weeks after end of treatment   |  |

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: For this outcome measure, there was no formal statistical comparison to an internal control group. Instead, overall responses were estimated using point and interval estimation and the SVR12 rate was compared with an historical control of simeprevir and PegIFN/RBV treatment in subjects with HCV genotype 1b infection and advanced fibrosis or compensated cirrhosis (Cohort 1).

| End point values                 | 12 Weeks Prior Amendment | 12 Weeks Post Amendment | 24 Weeks Extension    |  |
|----------------------------------|--------------------------|-------------------------|-----------------------|--|
| Subject group type               | Reporting group          | Reporting group         | Reporting group       |  |
| Number of subjects analysed      | 17                       | 25                      | 64                    |  |
| Units: percentage of subjects    |                          |                         |                       |  |
| number (confidence interval 95%) | 70.6 (44.04 to 89.69)    | 100 (86.28 to 100)      | 93.8 (84.76 to 98.27) |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects With Sustained Virologic Response 4 Weeks After end of Study Drug Treatment (SVR4)



|  |   |
|--|---|
| End point title  | Percentage of Subjects With Sustained Virologic Response 4 Weeks After end of Study Drug Treatment (SVR4) |
| End point description:<br>Subjects were considered to have reached SVR4, if 4 weeks after the actual EOT, HCV RNA was <LLOQ (detectable or undetectable). The ITT analysis set is defined as all subjects who received at least one dose of simeprevir or daclatasvir. |   |
| End point type   | Secondary   |
| End point timeframe:<br>At 4 weeks after actual EOT  |   |

| End point values                 | 12 Weeks Prior Amendment | 12 Weeks Post Amendment | 24 Weeks Extension    |  |
|----------------------------------|--------------------------|-------------------------|-----------------------|--|
| Subject group type               | Reporting group          | Reporting group         | Reporting group       |  |
| Number of subjects analysed      | 17                       | 25                      | 64                    |  |
| Units: percentage of subjects    |                          |                         |                       |  |
| number (confidence interval 95%) | 70.6 (44.04 to 89.69)    | 100 (86.28 to 100)      | 93.8 (84.76 to 98.27) |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects With SVR 24 Weeks After end of Study Drug Treatment (SVR 24)

|  |   |
|--|---|
| End point title  | Percentage of Subjects With SVR 24 Weeks After end of Study Drug Treatment (SVR 24) |
| End point description:<br>Subjects were considered to have reached SVR24, if 24 weeks after the actual EOT, HCV RNA was <LLOQ (detectable or undetectable). The ITT analysis set is defined as all subjects who received at least one dose of simeprevir or daclatasvir. |   |
| End point type   | Secondary   |
| End point timeframe:<br>At 24 weeks after actual EOT   |   |

| End point values                 | 12 Weeks Prior Amendment | 12 Weeks Post Amendment | 24 Weeks Extension    |  |
|----------------------------------|--------------------------|-------------------------|-----------------------|--|
| Subject group type               | Reporting group          | Reporting group         | Reporting group       |  |
| Number of subjects analysed      | 17                       | 25                      | 64                    |  |
| Units: percentage of subjects    |                          |                         |                       |  |
| number (confidence interval 95%) | 70.6 (44.04 to 89.69)    | 100 (86.28 to 100)      | 93.8 (84.76 to 98.27) |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects With On-treatment Failure

|                 |  |
|-----------------|--|
| End point title | Percentage of Subjects With On-treatment Failure |
|-----------------|--|

End point description:

Subjects were considered on-treatment failures if they did not achieve SVR12 and had (confirmed) detectable HCV RNA, i.e., <LLOQ detectable or greater than equal to ( $\geq$ ) LLOQ at EOT. The ITT analysis set is defined as all subjects who received at least one dose of simeprevir or daclatasvir.

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

End point timeframe:

Up to Week 24 after actual EOT

| End point values              | 12 Weeks Prior Amendment | 12 Weeks Post Amendment | 24 Weeks Extension |  |
|-------------------------------|--------------------------|-------------------------|--------------------|--|
| Subject group type            | Reporting group          | Reporting group         | Reporting group    |  |
| Number of subjects analysed   | 17                       | 25                      | 64                 |  |
| Units: percentage of subjects |                          |                         |                    |  |
| number (not applicable)       | 29.4                     | 0                       | 4.7                |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects With Viral Breakthrough

|                 |  |
|-----------------|--|
| End point title | Number of Subjects With Viral Breakthrough |
|-----------------|--|

End point description:

Subjects were considered to have had viral breakthrough if they had a confirmed greater than ( $>$ ) 1.0 log<sub>10</sub> international units/milliliter (IU/mL) increase in HCV RNA from nadir OR confirmed HCV RNA  $>100$  IU/mL while previously having achieved HCV RNA <LLOQ when on study treatment. The ITT analysis set is defined as all subjects who received at least one dose of simeprevir or daclatasvir.

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

End point timeframe:

Up to Week 24

| End point values            | 12 Weeks Prior Amendment | 12 Weeks Post Amendment | 24 Weeks Extension |  |
|-----------------------------|--------------------------|-------------------------|--------------------|--|
| Subject group type          | Reporting group          | Reporting group         | Reporting group    |  |
| Number of subjects analysed | 17                       | 25                      | 64                 |  |
| Units: subjects             | 4                        | 0                       | 3                  |  |

### Statistical analyses

No statistical analyses for this end point

---

**Secondary: Number of Subjects With Viral Relapse**

---

|                 |                                       |
|-----------------|---------------------------------------|
| End point title | Number of Subjects With Viral Relapse |
|-----------------|---------------------------------------|

End point description:

Subjects were considered to have had viral relapse if they did not achieve SVR12 and met the following conditions: had HCV RNA <LLOQ (undetectable) at EOT and had HCV RNA  $\geq$ LLOQ during the follow-up period. The ITT analysis set is defined as all subjects who received at least one dose of simeprevir or daclatasvir.

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

End point timeframe:

Up to Week 24 after actual EOT

---

| End point values            | 12 Weeks Prior Amendment | 12 Weeks Post Amendment | 24 Weeks Extension |  |
|-----------------------------|--------------------------|-------------------------|--------------------|--|
| Subject group type          | Reporting group          | Reporting group         | Reporting group    |  |
| Number of subjects analysed | 17                       | 25                      | 64                 |  |
| Units: subjects             | 0                        | 0                       | 1                  |  |

---

**Statistical analyses**

---

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to 24 weeks

Adverse event reporting additional description:

Total number of subjects at risk reported in the 12-24 weeks were the same subjects who continued the 24 weeks extension period after completion of 1-12 weeks treatment phase (up to Day 88).

|                 |                |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 18.0 |
|--------------------|------|

### Reporting groups

|                       |            |
|-----------------------|------------|
| Reporting group title | 1-12 Weeks |
|-----------------------|------------|

Reporting group description:

Simeprevir 150 mg once daily as an oral capsule in combination with Daclatasvir 60 mg once daily as an oral tablet for subjects who has AEs that started before or on Day 88 on treatment.

|                       |             |
|-----------------------|-------------|
| Reporting group title | 12-24 Weeks |
|-----------------------|-------------|

Reporting group description:

Simeprevir 150 mg once daily as an oral capsule in combination with Daclatasvir 60 mg once daily as an oral tablet for subjects who has adverse events (AEs) that started after Day 88 on treatment.

| Serious adverse events                            | 1-12 Weeks      | 12-24 Weeks    |  |
|---|-----------------|----------------|--|
| Total subjects affected by serious adverse events |                 |                |  |
| subjects affected / exposed                       | 4 / 106 (3.77%) | 3 / 64 (4.69%) |  |
| number of deaths (all causes)                     | 0               | 0              |  |
| number of deaths resulting from adverse events    |                 |                |  |
| Injury, poisoning and procedural complications    |                 |                |  |
| Fall  |                 |                |  |
| alternative assessment type: Systematic           |                 |                |  |
| subjects affected / exposed                       | 0 / 106 (0.00%) | 1 / 64 (1.56%) |  |
| occurrences causally related to treatment / all   | 0 / 0           | 0 / 1          |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0          |  |
| Wound Haemorrhage                                 |                 |                |  |
| alternative assessment type: Systematic           |                 |                |  |
| subjects affected / exposed                       | 0 / 106 (0.00%) | 1 / 64 (1.56%) |  |
| occurrences causally related to treatment / all   | 0 / 0           | 0 / 1          |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0          |  |
| Cardiac disorders                                 |                 |                |  |
| Atrial Fibrillation                               |                 |                |  |

|  |                 |                |  |
|--|-----------------|----------------|--|
| alternative assessment type:<br>Systematic         |                 |                |  |
| subjects affected / exposed                        | 1 / 106 (0.94%) | 0 / 64 (0.00%) |  |
| occurrences causally related to<br>treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0          |  |
| Pericarditis                                       |                 |                |  |
| alternative assessment type:<br>Systematic         |                 |                |  |
| subjects affected / exposed                        | 0 / 106 (0.00%) | 1 / 64 (1.56%) |  |
| occurrences causally related to<br>treatment / all | 0 / 0           | 0 / 2          |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0          |  |
| Gastrointestinal disorders                         |                 |                |  |
| Abdominal Pain                                     |                 |                |  |
| alternative assessment type:<br>Systematic         |                 |                |  |
| subjects affected / exposed                        | 1 / 106 (0.94%) | 0 / 64 (0.00%) |  |
| occurrences causally related to<br>treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0          |  |
| Vomiting   |                 |                |  |
| alternative assessment type:<br>Systematic         |                 |                |  |
| subjects affected / exposed                        | 1 / 106 (0.94%) | 0 / 64 (0.00%) |  |
| occurrences causally related to<br>treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0          |  |
| Hepatobiliary disorders                            |                 |                |  |
| Cholelithiasis                                     |                 |                |  |
| alternative assessment type:<br>Systematic         |                 |                |  |
| subjects affected / exposed                        | 0 / 106 (0.00%) | 1 / 64 (1.56%) |  |
| occurrences causally related to<br>treatment / all | 0 / 0           | 0 / 1          |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0          |  |
| Skin and subcutaneous tissue disorders             |                 |                |  |
| Photosensitivity Reaction                          |                 |                |  |
| alternative assessment type:<br>Systematic         |                 |                |  |
| subjects affected / exposed                        | 1 / 106 (0.94%) | 0 / 64 (0.00%) |  |
| occurrences causally related to<br>treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0          |  |
| Renal and urinary disorders                        |                 |                |  |
| Acute Kidney Injury                                |                 |                |  |

|  |                 |                |  |
|--|-----------------|----------------|--|
| alternative assessment type:<br>Systematic         |                 |                |  |
| subjects affected / exposed                        | 1 / 106 (0.94%) | 0 / 64 (0.00%) |  |
| occurrences causally related to<br>treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0          |  |

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

| <b>Non-serious adverse events</b>                        | 1-12 Weeks        | 12-24 Weeks    |  |
|--|-------------------|----------------|--|
| Total subjects affected by non-serious<br>adverse events |                   |                |  |
| subjects affected / exposed                              | 44 / 106 (41.51%) | 2 / 64 (3.13%) |  |
| Nervous system disorders                                 |                   |                |  |
| Headache   |                   |                |  |
| alternative assessment type:<br>Systematic               |                   |                |  |
| subjects affected / exposed                              | 16 / 106 (15.09%) | 0 / 64 (0.00%) |  |
| occurrences (all)  | 20                | 0              |  |
| General disorders and administration<br>site conditions  |                   |                |  |
| Asthenia   |                   |                |  |
| alternative assessment type:<br>Systematic               |                   |                |  |
| subjects affected / exposed                              | 14 / 106 (13.21%) | 1 / 64 (1.56%) |  |
| occurrences (all)  | 14                | 1              |  |
| Fatigue  |                   |                |  |
| alternative assessment type:<br>Systematic               |                   |                |  |
| subjects affected / exposed                              | 16 / 106 (15.09%) | 1 / 64 (1.56%) |  |
| occurrences (all)  | 16                | 2              |  |
| Skin and subcutaneous tissue disorders                   |                   |                |  |
| Pruritus   |                   |                |  |
| alternative assessment type:<br>Systematic               |                   |                |  |
| subjects affected / exposed                              | 11 / 106 (10.38%) | 0 / 64 (0.00%) |  |
| occurrences (all)  | 11                | 0              |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date          | Amendment   |
|---------------|---|
| 02 March 2015 | The amendment INT-2 included the following changes: Investigators had suggested to expand the study to include additional patient populations, in particular patients who had less advanced liver fibrosis (corresponding to METAVIR F0 F2), those who had hepatitis C virus (HCV) genotype 4, and those who had human immunodeficiency virus (HIV) or HCV coinfection. For both patient populations, interferon (IFN) -free options were still limited either due to restricted access or to lack of data. Both simeprevir and daclatasvir have individually shown to be active against HCV genotype 4 in Phase 3 clinical studies with pegylated interferon (PegIFN) and ribavirin (RBV), and are approved for the treatment of adult patients with HCV genotype 4. Increasing evidence indicated that the efficacy and safety of IFN free therapy was similar in HCV-infected patients with or without HIV coinfection. Hepatitis C virus therapy in HIV-/HCV-coinfected patients therefore had to follow the same treatment recommendations as in mono-infected patients, provided that potential drug interactions between HIV and HCV treatments were considered. Patients who had mild fibrosis, HCV genotype 4, and/or HCV/HIV coinfection continue to be under treated patient populations to understand the efficacy and safety of treatment with simeprevir in combination with daclatasvir. Additionally, the period after the end of therapy during which subjects were required to adhere to contraception requirements and sperm donation restrictions was extended, based on nonclinical embryotoxicity and teratogenicity information for daclatasvir. |
| 01 June 2015  | The amendment INT-3 included the following changes: 1) Sponsor's decision to discontinue Cohort 2 (METAVIR F0-F2 treatment-naïve subjects who had genotype 1b infection) due to prompted concern that viral breakthrough could also be observed in subjects with HCV genotype 1b infection and mild-to-moderate fibrosis because Viral breakthroughs were observed in the early phase of Cohort 1 (METAVIR F3/F4 treatment naïve subjects with HCV genotype 1b infection), 2) Discontinuation of Cohort 3 due to the observed cases of viral breakthrough in a HCV genotype 1b population without baseline mutations L31M/V and Y93H, it could no longer be excluded with certainty that viral breakthrough could also be observed in HCV genotype 4, 3) Since no subjects with HIV were enrolled, information related to inclusion of HIV subjects, including concomitant therapy allowed, was no longer necessary, 4) collection of blood samples and analyses of pharmacokinetics, HIV viral load, and efficacy related to HIV and combination antiretroviral therapy (cART) were not collected/performed at time points after screening, 5) Extended required wash-out period for amiodarone to 120 days prior to baseline due its long half life, 6) Physical examination data were not recorded on the electronic case report form (eCRF); therefore no analyses of the data were performed, 7) clarified statistical methods for the primary analysis for Cohort 1, 8) Minor errors were noted or minor editorial changes made.  |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to the implementation of Amendment 3 while treatment was ongoing, subjects received different treatment durations in a nonrandomized fashion. Therefore, no firm conclusions could be made about the optimal treatment duration for specific subjects.

