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, clinicaltrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Janssen-Cilag International NV, 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-naive, 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
Arm title	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.

Arm title	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.

Arm title	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.

Number of subjects in period 1	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:	
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:	
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:	
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 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 Units: years			
median	53	64	59
full range (min-max)	21 to 82	25 to 83	26 to 83
Title for Gender Units: subjects			
Female	5	11	27
Male	12	14	37

Reporting group values	Total		
Number of subjects	106		
Title for AgeCategorical 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 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:	
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:	
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:	
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)[1]
End point description:	
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:	
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:

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:

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:

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:

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 (>=) 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 log10 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 >=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: Systematic			
subjects affected / exposed	1 / 106 (0.94%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 106 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal Pain			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 106 (0.94%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 106 (0.94%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
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	
Skin and subcutaneous tissue disorders			
Photosensitivity Reaction			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 106 (0.94%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute Kidney Injury			

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

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

Non-serious adverse events	1-12 Weeks	12-24 Weeks	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	44 / 106 (41.51%)	2 / 64 (3.13%)	
Nervous system disorders			
Headache			
alternative assessment type: Systematic			
subjects affected / exposed	16 / 106 (15.09%)	0 / 64 (0.00%)	
occurrences (all)	20	0	
General disorders and administration site conditions			
Asthenia			
alternative assessment type: Systematic			
subjects affected / exposed	14 / 106 (13.21%)	1 / 64 (1.56%)	
occurrences (all)	14	1	
Fatigue			
alternative assessment type: 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: 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-naive 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.