Clinical trial results:
A Phase 3, Multicentre, Open-Label, Single-Arm Study to Investigate the Efficacy and Safety of a 12-Week Regimen of Simeprevir in Combination with Sofosbuvir in Treatment naïve or -Experienced Subjects with Chronic Genotype 4 Hepatitis C Virus Infection

Summary

EudraCT number	2014-003446-27
Trial protocol	ES
Global end of trial date	23 December 2015

Results information

Result version number	v1 (current)
This version publication date	10 November 2016
First version publication date	10 November 2016

Trial information

Trial identification

Sponsor protocol code	TMC435HPC3021

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02250807
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen R&D Ireland
Sponsor organisation address	Turnhoutseweg 30, 2340 Beerse, Belgium,
Public contact	Global Clinical Operations, Janssen R&D Ireland, ClinicalTrialsEU@its.jnj.com
Scientific contact	Global Clinical Operations, Janssen R&D Ireland, 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	23 December 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 December 2015
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 show superiority of simeprevir (SMV) 150 milligram (mg) once daily in combination with sofosbuvir (SOF) 400 mg once daily for 12 weeks versus a historical control, with respect to the proportion of participants with sustained virologic response 12 (SVR12) in the overall population.

Protection of trial subjects:

Safety evaluations for this study included the monitoring of adverse events (AEs); laboratory tests (hematology, urinalysis and serum chemistry); vital sign measurements and physical examinations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 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	Spain: 40
Worldwide total number of subjects	40
EEA total number of subjects	40

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)	38
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study was conducted from 7 January 2015 to 23 December 2015. 40 participants were enrolled in the study and received treatment.

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

Arm title	SMV+SOF 12 Weeks

Arm description:

Participants received oral capsule of simeprevir (SMV) 150 milligram (mg) and an oral tablet of sofosbuvir (SOF) 400 mg, once a day from Day 1 through Week 12.

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:

Participants received oral capsule of SMV 150 mg once a day from Day 1 through Week 12.

Investigational medicinal product name	Sofosbuvir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received oral tablet of SOF 400 mg, once a day from Day 1 through Week 12.

Number of subjects in period 1	SMV+SOF 12 Weeks
Started	40
Completed	40

Baseline characteristics

Reporting groups	
Reporting group title	SMV+SOF 12 Weeks
Reporting group description:	
Participants received oral capsule of simeprevir (SMV) 150 milligram (mg) and an oral tablet of sofosbuvir (SOF) 400 mg, once a day from Day 1 through Week 12.	

Reporting group values	SMV+SOF 12 Weeks	Total	
Number of subjects	40	40	
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	38	38	
From 65 to 84 years	2	2	
85 years and over	0	0	
Title for AgeContinuous Units: years			
median	51		
full range (min-max)	29 to 69	-	
Title for Gender Units: subjects			
Female	11	11	
Male	29	29	

End points

End points reporting groups

Reporting group title	SMV+SOF 12 Weeks

Reporting group description:

Participants received oral capsule of simeprevir (SMV) 150 milligram (mg) and an oral tablet of sofosbuvir (SOF) 400 mg, once a day from Day 1 through Week 12.

Primary: Percentage of Participants With Sustained Virologic Response 12 Weeks after End of Treatment (EOT) (SVR12)

End point title	Percentage of Participants With Sustained Virologic Response 12 Weeks after End of Treatment (EOT) (SVR12)[1]

End point description:

SVR12 is defined as the percentage of participants with hepatitis C virus ribonucleic acid (HCV RNA) less than (<) lower limit of quantification (LLOQ; 15 international unit per milliliter [IU/mL]) detectable or undetectable 12 weeks after actual EOT. Intent-to-treat (ITT) population included all randomized participants who received at least 1 dose of study medication (SMV and/or SOF).

End point type	Primary

End point timeframe:

12 weeks after EOT

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: Descriptive Statistical analysis was performed for the outcome measure.

End point values	SMV+SOF 12 Weeks			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: percentage of participants				
number (confidence interval 95%)	100 (91.2 to 100)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Sustained Virologic Response 4 Weeks After End of Therapy (SVR4)

End point title	Percentage of Participants With Sustained Virologic Response 4 Weeks After End of Therapy (SVR4)

End point description:

SVR4 is defined as the percentage of participants with hepatitis C virus ribonucleic acid (HCV RNA) less than (<) lower limit of quantification (LLOQ; 15 international unit per milliliter [IU/mL]) detectable or undetectable 4 weeks after actual EOT. ITT population included all randomized participants who received at least 1 dose of study medication (SMV and/or SOF).

End point type	Secondary

End point timeframe:

4 weeks after EOT

End point values	SMV+SOF 12 Weeks			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: percentage of participants				
number (confidence interval 95%)	100 (91.2 to 100)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Sustained Virologic Response 24 Weeks After End of Therapy (SVR24)

End point title	Percentage of Participants With Sustained Virologic Response 24 Weeks After End of Therapy (SVR24)

End point description:

Participants were considered to have reached SVR24, if at the time point of SVR24 (that is [i.e.], 24 weeks after the actual end of treatment [EOT]) the following condition has been met: HCV RNA < lower limit of quantification (LLOQ), i.e., 15 IU/mL, detectable or undetectable. ITT population included all randomized participants who received at least 1 dose of study medication (SMV and/or SOF).

End point type	Secondary

End point timeframe:

At 24 weeks after EOT

End point values	SMV+SOF 12 Weeks			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: percentage of participants				
number (confidence interval 95%)	100 (91.2 to 100)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With On-treatment Virologic Response of Hepatitis C Virus (HCV) Ribonucleic Acid (RNA)

End point title	Percentage of Participants With On-treatment Virologic Response of Hepatitis C Virus (HCV) Ribonucleic Acid (RNA)

End point description:

Percentage of participants with HCV RNA less than (<) 15 IU/mL undetectable or detectable or

detectable /undetectable at specific time points were observed. ITT population included all randomized participants who received at least 1 dose of study medication (SMV and/or SOF).

End point type	Secondary

End point timeframe:

Week 2, 3, 4, 12 and EOT

End point values	SMV+SOF 12 Weeks			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: percentage of participants				
number (not applicable)				
Week 2: < 100 IU/mL	87.5			
Week 2: < 15 IU/mL undetectable/detectable	40			
Week 2: < 15 IU/mL undetectable	17.5			
Week 3: < 100 IU/mL	100			
Week 3: < 15 IU/mL undetectable/detectable	82.5			
Week 3: < 15 IU/mL undetectable	40			
Week 4: < 100 IU/mL	100			
Week 4: < 15 IU/mL undetectable/detectable	87.5			
Week 4: < 15 IU/mL undetectable (RVR)	65			
Week 12: < 100 IU/mL	100			
Week 12: < 15 IU/mL undetectable/detectable	100			
Week 12: < 15 IU/mL undetectable	100			
End of Treatment (EOT): < 100 IU/mL	100			
EOT: < 15 IU/mL undetectable/detectable	100			
EOT: < 15 IU/mL undetectable	100			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With On-treatment Failure

End point title	Percentage of Participants With On-treatment Failure

End point description:

Participants were considered on-treatment failures if they have at EOT (confirmed) detectable HCV RNA, i.e., <LLOQ detectable or >=LLOQ. ITT population included all randomized participants who received at least 1 dose of study medication (SMV and/or SOF).

End point type	Secondary

End point timeframe:

Through 12 weeks (EOT)

End point values	SMV+SOF 12 Weeks			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: percentage of participants				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Viral Breakthrough

End point title	Percentage of Participants With Viral Breakthrough

End point description:

Participants with confirmed >1.0 log10 increase in HCV RNA from nadir whilst on study therapy or confirmed HCV RNA >100 IU/mL whilst on study therapy in participants who had previously achieved HCV RNA <LLOQ. ITT population included all randomized participants who received at least 1 dose of study medication (SMV and/or SOF).

End point type	Secondary

End point timeframe:

Up to follow-up Week 24

End point values	SMV+SOF 12 Weeks			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: percentage of participants				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Viral Relapse

End point title	Percentage of Participants With Viral Relapse

End point description:

Participants were considered to have viral relapse if they did not achieve SVR12 and meet the following conditions: 1) at EOT, HCV RNA less than (<)LLOQ, undetectable, and 2) during the follow-up period, HCV RNA greater than or equal to (>=)LLOQ. ITT population included all randomized participants who received at least 1 dose of study medication (SMV and/or SOF).

End point type	Secondary

End point timeframe:
Up to follow-up week 24

End point values	SMV+SOF 12 Weeks			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: percentage of participants				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Up to EOT (Week 12)	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.0
Reporting groups	
Reporting group title	SMV+SOF 12 Wks
Reporting group description: Participants received oral capsule of simeprevir (SMV) 150 milligram (mg) and an oral tablet of sofosbuvir (SOF) 400 mg, once a day from Day 1 through Week 12.	

Serious adverse events	SMV+SOF 12 Wks		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 40 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	SMV+SOF 12 Wks		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 40 (42.50%)		
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 40 (20.00%)		
occurrences (all)	16		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		

Respiratory, thoracic and mediastinal disorders			
Catarrh			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Rash			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 April 2015	The amendment 1 was reported as an "urgent safety measure" to disallow the use of amiodarone from Screening onwards until the end of the treatment period to protect the safety of the participants. On 24 March 2015, the United States Food and Drug Administration (FDA) issued warnings on the risk of bradycardia and cardiac arrest when the antiarrhythmic drug amiodarone is used together with sofosbuvir (SOF) or the fixed-dose combination SOF/ledipasvir in combination with another direct-acting antiviral (DAA) for the treatment of hepatitis C virus (HCV) infection. The FDA recommended that health care professionals should not prescribe SOF combined with another DAA, such as simeprevir (SMV), with amiodarone. Therefore, the sponsor considered it necessary to disallow the co-administration of amiodarone while participants were treated with the combination of SMV+SOF in this study, to avoid the risk of potential drug interactions.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported