Clinical trial results:
A Phase 2, 2-panel, Open-label, Randomized Study to Investigate the Pharmacokinetic Interactions Between Simeprevir and Ledipasvir in a Treatment Regimen Consisting of Simeprevir, Sofosbuvir, and Ledipasvir in Treatment-naïve Subjects With Chronic Hepatitis C Virus Genotype 1 Infection

Summary

EudraCT number	2015-000459-25
Trial protocol	BE
Global end of trial date	27 January 2016

Results information

Result version number	v1 (current)
This version publication date	01 January 2017
First version publication date	01 January 2017

Trial information

Trial identification

Sponsor protocol code	TMC435HPC2017

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02421211
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen Sciences Ireland UC
Sponsor organisation address	Eastgate, Little Island, Cork, Ireland, Belgium, IE-CO T45 A363
Public contact	Clinical Registry Group, Janssen Sciences Ireland UC, clinicaltrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Janssen Sciences Ireland UC, 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	27 January 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 January 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objectives of this study were to evaluate the effect of multiple-dose ledipasvir (LDV) 90 milligram (mg) once daily given in combination with sofosbuvir (SOF) 400 mg once daily on the steady-state pharmacokinetics (PK) of SMV 150 mg once daily in chronic hepatitis C virus (HCV) genotype 1 infected participants and to evaluate the effect of multiple-dose SMV 150 mg once daily on the steady-state PK of LDV 90 mg once daily given in combination with SOF 400 mg once daily in chronic HCV genotype 1 infected participants.

Protection of trial subjects:

Safety evaluations for this study included the monitoring of adverse events (AEs) (including specific toxicities), clinical laboratory tests (hematology, serum chemistry, coagulation, and urinalysis), electrocardiograms (ECGs), vital sign measurements and physical examinations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 May 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: 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)	39
From 65 to 84 years	1

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 41 participants were enrolled in the study. Among them 40 participants (20 per panel) were randomized and treated. One participant was early terminated from the study, due to withdrawal of consent before randomization to study drug. All randomized participants received study drug and were included in the intent to treat (ITT) population.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Panel 1: SMV 150mg+LDV 90mg/SOF 400mg - 10 Weeks

Arm description:

Participants (Intent-to-treat [ITT] population) received simeprevir (SMV) 150 milligram (mg) capsule and sofosbuvir (SOF) 400 mg tablet, orally, once daily from Day 1 until Day 14. From Day 15 until Day 70, participants received SMV 150 mg capsule and a fixed dose combination (FDC) tablet of 90 mg Ledipasvir (LDV)/400 mg SOF, orally and once daily. ITT population is defined as all enrolled participants who took at least 1 dose of SMV, LDV, or SOF.

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 SMV 150 mg capsule orally and once daily, from Day 1 until Day 70.

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

Dosage and administration details:

Participants received SOF 400 mg tablet, orally, once daily from Day 1 until Day 14 and a fixed dose combination (FDC) tablet of 90 mg Ledipasvir (LDV)/400 mg SOF, orally and once daily from Day 15 until Day 70.

Investigational medicinal product name	Ledipasvir/Sofosbuvir- FDC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received a fixed dose combination tablet of 90 mg LDV/400 mg SOF, orally and once daily from Day 15 until Day 70.

Arm title	Panel 2: SMV 150mg+LDV 90mg/SOF 400mg - 8 Weeks

Arm description:

Participants (ITT population) received FDC tablet of 90 mg LDV/400 mg SOF, orally, once daily from Day 1 until Day 14. From Day 15 until Day 56, participants received SMV 150 mg capsule and a FDC tablet of 90 mg LDV/400 mg SOF, orally and once daily.

Arm type	Experimental
Investigational medicinal product name	Ledipasvir/Sofosbuvir - FDC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received FDC tablet of 90 mg LDV/400 mg SOF, orally, once daily from Day 1 until Day 56.

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

Dosage and administration details:

Participants received SMV 150 mg capsule orally and once daily from Day 15 until Day 56.

Number of subjects in period 1	Panel 1: SMV 150mg+LDV 90mg/SOF 400mg - 10 Weeks	Panel 2: SMV 150mg+LDV 90mg/SOF 400mg - 8 Weeks
Started	20	20
Completed	20	20

Baseline characteristics

Reporting groups	
Reporting group title	Panel 1: SMV 150mg+LDV 90mg/SOF 400mg - 10 Weeks
Reporting group description:	
Participants (Intent-to-treat [ITT] population) received simeprevir (SMV) 150 milligram (mg) capsule and sofosbuvir (SOF) 400 mg tablet, orally, once daily from Day 1 until Day 14. From Day 15 until Day 70, participants received SMV 150 mg capsule and a fixed dose combination (FDC) tablet of 90 mg Ledipasvir (LDV)/400 mg SOF, orally and once daily. ITT population is defined as all enrolled participants who took at least 1 dose of SMV, LDV, or SOF.	
Reporting group title	Panel 2: SMV 150mg+LDV 90mg/SOF 400mg - 8 Weeks
Reporting group description:	
Participants (ITT population) received FDC tablet of 90 mg LDV/400 mg SOF, orally, once daily from Day 1 until Day 14. From Day 15 until Day 56, participants received SMV 150 mg capsule and a FDC tablet of 90 mg LDV/400 mg SOF, orally and once daily.	

Reporting group values	Panel 1: SMV 150mg+LDV 90mg/SOF 400mg - 10 Weeks	Panel 2: SMV 150mg+LDV 90mg/SOF 400mg - 8 Weeks	Total
Number of subjects	20	20	40
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	19	20	39
From 65 to 84 years	1	0	1
85 years and over	0	0	0
Title for AgeContinuous Units: years			
median	50.5	51	
full range (min-max)	25 to 70	26 to 62	-
Title for Gender Units: subjects			
Female	12	10	22
Male	8	10	18

End points

End points reporting groups

Reporting group title	Panel 1: SMV 150mg+LDV 90mg/SOF 400mg - 10 Weeks
Reporting group description:	
Participants (Intent-to-treat [ITT] population) received simeprevir (SMV) 150 milligram (mg) capsule and sofosbuvir (SOF) 400 mg tablet, orally, once daily from Day 1 until Day 14. From Day 15 until Day 70, participants received SMV 150 mg capsule and a fixed dose combination (FDC) tablet of 90 mg Ledipasvir (LDV)/400 mg SOF, orally and once daily. ITT population is defined as all enrolled participants who took at least 1 dose of SMV, LDV, or SOF.	
Reporting group title	Panel 2: SMV 150mg+LDV 90mg/SOF 400mg - 8 Weeks
Reporting group description:	
Participants (ITT population) received FDC tablet of 90 mg LDV/400 mg SOF, orally, once daily from Day 1 until Day 14. From Day 15 until Day 56, participants received SMV 150 mg capsule and a FDC tablet of 90 mg LDV/400 mg SOF, orally and once daily.	
Subject analysis set title	Panel 1: 150 mg SMV + 400 mg SOF (Day 14)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The Intention-to-treat (ITT) analysis set is defined as all enrolled participants who took at least 1 dose of simeprevir (SMV), ledipasvir (LDV), or sofosbuvir (SOF).	
Subject analysis set title	Panel 1: SMV 150mg+LDV 90mg/SOF 400mg (Day 28)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT analysis set is defined as all enrolled participants who took at least 1 dose of SMV, LDV, or SOF.	
Subject analysis set title	Panel 2: 90/400 mg LDV/SOF (Day 14)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT analysis set is defined as all enrolled participants who took at least 1 dose of SMV, LDV, or SOF.	
Subject analysis set title	Panel 2: SMV 150mg+LDV 90mg/SOF 400mg (Day 28)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT analysis set is defined as all enrolled participants who took at least 1 dose of SMV, LDV, or SOF.	

Primary: Minimum Plasma Concentration (Cmin) of Simeprevir (SMV)

End point title	Minimum Plasma Concentration (Cmin) of Simeprevir (SMV)
End point description:	
The Cmin is the minimum observed plasma concentration. The analysis was done on the Intent-to-treat (ITT) population.	
End point type	Primary
End point timeframe:	
Predose, 0.5, 1, 2, 4, 6, 8, 10, 12, 18, and 24 hours postdose on Day 14 and Day 28	

End point values	Panel 1: 150 mg SMV + 400 mg SOF (Day 14)	Panel 1: SMV 150mg+LDV 90mg/SOF 400mg (Day 28)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	20		
Units: nanogram per Milliliters (ng/mL)				
arithmetic mean (standard deviation)	2411 (± 3778)	6701 (± 4179)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Panel 1: SMV 150mg+LDV 90mg/SOF 400mg (Day 28) v Panel 1: 150 mg SMV + 400 mg SOF (Day 14)
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Least Square (LS) means ratio
Point estimate	4.7
Confidence interval	
level	90 %
sides	2-sided
lower limit	3.4
upper limit	6.5

Primary: Maximum Plasma Concentration (Cmax) of SMV

End point title	Maximum Plasma Concentration (Cmax) of SMV
End point description:	
The Cmax is the maximum observed plasma concentration. The analysis was done on the ITT population.	
End point type	Primary
End point timeframe:	
Predose, 0.5, 1, 2, 4, 6, 8, 10, 12, 18, and 24 hours postdose on Day 14 and Day 28	

End point values	Panel 1: 150 mg SMV + 400 mg SOF (Day 14)	Panel 1: SMV 150mg+LDV 90mg/SOF 400mg (Day 28)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	19[1]		
Units: ng/mL				
arithmetic mean (standard deviation)	6767 (± 6362)	13691 (± 7775)		

Notes:

[1] - Here 'N' signifies number of participants analysed for this outcome measure.

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Panel 1: SMV 150mg+LDV 90mg/SOF 400mg (Day 28) v Panel 1: 150 mg SMV + 400 mg SOF (Day 14)
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS means ratio
Point estimate	2.3
Confidence interval	
level	90 %
sides	2-sided
lower limit	2
upper limit	2.8

Primary: Area Under the Curve From Time Zero to End of Dosing Interval (AUCtau) of SMV

End point title	Area Under the Curve From Time Zero to End of Dosing Interval (AUCtau) of SMV

End point description:

The AUCtau is the measure of the plasma drug concentration from time zero to end of dosing interval. It is used to characterize drug absorption. The analysis was done on the ITT population.

End point type	Primary

End point timeframe:

Predose, 0.5, 1, 2, 4, 6, 8, 10, 12, 18, and 24 hours postdose on Day 14 and Day 28

End point values	Panel 1: 150 mg SMV + 400 mg SOF (Day 14)	Panel 1: SMV 150mg+LDV 90mg/SOF 400mg (Day 28)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	19[2]		
Units: nanogram hour per Milliliters (ng*h/mL)				
arithmetic mean (standard deviation)	100492 (± 115868)	243564 (± 159124)		

Notes:

[2] - Here 'N' signifies number of participants analysed for this outcome measure.

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Panel 1: SMV 150mg+LDV 90mg/SOF 400mg (Day 28) v Panel 1: 150 mg SMV + 400 mg SOF (Day 14)

Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS means ratio
Point estimate	3.1
Confidence interval	
level	90 %
sides	2-sided
lower limit	2.4
upper limit	3.8

Primary: Minimum Plasma Concentration (Cmin) of Ledipasvir (LDV)

End point title	Minimum Plasma Concentration (Cmin) of Ledipasvir (LDV)

End point description:

The Cmin is the minimum observed plasma concentration. The analysis was done on the ITT population.

End point type	Primary

End point timeframe:

Predose, 0.5, 1, 2, 4, 6, 8, 10, 12, 18, and 24 hours postdose on Day 14 and Day 28

End point values	Panel 2: 90/400 mg LDV/SOF (Day 14)	Panel 2: SMV 150mg+LDV 90mg/SOF 400mg (Day 28)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	18[3]		
Units: ng/mL				
arithmetic mean (standard deviation)	319 (± 178)	557 (± 307)		

Notes:

[3] - Here 'N' signifies number of participants analysed for this outcome measure.

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Panel 2: SMV 150mg+LDV 90mg/SOF 400mg (Day 28) v Panel 2: 90/400 mg LDV/SOF (Day 14)
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS means ratio
Point estimate	1.7
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.5
upper limit	2

Primary: Maximum Plasma Concentration (Cmax) of LDV

End point title	Maximum Plasma Concentration (Cmax) of LDV

End point description:

The Cmax is the maximum observed plasma concentration. The analysis was done on the ITT population.

End point type	Primary

End point timeframe:

Predose, 0.5, 1, 2, 4, 6, 8, 10, 12, 18, and 24 hours postdose on Day 14 and Day 28

End point values	Panel 2: 90/400 mg LDV/SOF (Day 14)	Panel 2: SMV 150mg+LDV 90mg/SOF 400mg (Day 28)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	17[4]		
Units: ng/mL				
arithmetic mean (standard deviation)	556 (± 270)	930 (± 466)		

Notes:

[4] - Here 'N' signifies number of participants analysed for this outcome measure.

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Panel 2: SMV 150mg+LDV 90mg/SOF 400mg (Day 28) v Panel 2: 90/400 mg LDV/SOF (Day 14)
Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS means ratio
Point estimate	1.6
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.4
upper limit	1.9

Primary: Area Under the Curve From Time Zero to End of Dosing Interval (AUCtau) of LDV

End point title	Area Under the Curve From Time Zero to End of Dosing Interval (AUCtau) of LDV

End point description:

AUCtau is defined as area under the analyte concentration versus time curve during dosing interval tau, calculated by linear-linear trapezoidal summation. The analysis was done on the ITT population.

End point type	Primary

End point timeframe:

Predose, 0.5, 1, 2, 4, 6, 8, 10, 12, 18, and 24 hours postdose on Day 14 and Day 28

End point values	Panel 2: 90/400 mg LDV/SOF (Day 14)	Panel 2: SMV 150mg+LDV 90mg/SOF 400mg (Day 28)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	17[5]		
Units: ng*h/mL				
arithmetic mean (standard deviation)	9868 (± 4930)	17435 (± 8772)		

Notes:

[5] - Here 'N' signifies number of participants analysed for this outcome measure.

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Panel 2: SMV 150mg+LDV 90mg/SOF 400mg (Day 28) v Panel 2: 90/400 mg LDV/SOF (Day 14)
Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS means ratio
Point estimate	1.7
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.6
upper limit	2

Secondary: Trough Plasma Concentration (Ctrough) of SMV

End point title	Trough Plasma Concentration (Ctrough) of SMV

End point description:

The (Ctrough) is the plasma concentration before dosing or at the end of the dosing interval of any dose other than the first dose in a multiple dosing regimen. The analysis was done on the ITT population.

End point type	Secondary

End point timeframe:

Predose on Day 14 and Day 28

End point values	Panel 1: 150 mg SMV + 400 mg SOF (Day 14)	Panel 1: SMV 150mg+LDV 90mg/SOF 400mg (Day 28)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19[6]	20		
Units: ng/mL				
arithmetic mean (standard deviation)	3059 (± 4236)	8453 (± 6455)		

Notes:

[6] - Here 'N' signifies number of participants analysed for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach Maximum Plasma Concentration (Tmax) of SMV

End point title	Time to Reach Maximum Plasma Concentration (Tmax) of SMV

End point description:

The Tmax is defined as actual sampling time to reach maximum observed analyte concentration. The analysis was done on the ITT population.

End point type	Secondary

End point timeframe:

Predose, 0.5, 1, 2, 4, 6, 8, 10, 12, 18, and 24 hours postdose on Day 14 and Day 28

End point values	Panel 1: 150 mg SMV + 400 mg SOF (Day 14)	Panel 1: SMV 150mg+LDV 90mg/SOF 400mg (Day 28)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	19[7]		
Units: hour (H)				
median (full range (min-max))	6 (4 to 12)	6 (0.47 to 10)		

Notes:

[7] - Here 'N' signifies number of participants analysed for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Average Plasma Concentration at Steady State (Cavg,ss) of SMV

End point title	Average Plasma Concentration at Steady State (Cavg,ss) of SMV

End point description:

The Cavg,ss is calculated as area under the plasma concentration-time curve during a dosing Interval (AUC[tau]) divided by the dosing interval (tau). The analysis was done on the ITT population.

End point type	Secondary

End point timeframe:

Predose, 0.5, 1, 2, 4, 6, 8, 10, 12, 18, and 24 hours postdose on Day 14 and Day 28

End point values	Panel 1: 150 mg SMV + 400 mg SOF (Day 14)	Panel 1: SMV 150mg+LDV 90mg/SOF 400mg (Day 28)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	19[8]		
Units: ng/mL				
arithmetic mean (standard deviation)	4196 (± 4833)	10139 (± 6628)		

Notes:

[8] - Here 'N' signifies number of participants analysed for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Fluctuation Index (FI) of SMV

End point title	Fluctuation Index (FI) of SMV

End point description:

Fluctuation index is defined as percentage fluctuation (variation between maximum and minimum concentration at steady state), calculated as: 100*([Cmax Cmin]/Cavg). The analysis was done on the ITT population.

End point type	Secondary

End point timeframe:

Predose, 0.5, 1, 2, 4, 6, 8, 10, 12, 18, and 24 hours postdose on Day 14 and Day 28

End point values	Panel 1: 150 mg SMV + 400 mg SOF (Day 14)	Panel 1: SMV 150mg+LDV 90mg/SOF 400mg (Day 28)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	19[9]		
Units: percentage of fluctuation				
arithmetic mean (standard deviation)	144 (± 55.5)	84.4 (± 36.5)		

Notes:

[9] - Here 'N' signifies number of participants analysed for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Plasma Concentration (Ctrough) of (LDV)

End point title	Trough Plasma Concentration (Ctrough) of (LDV)

End point description:

The (Ctrough) is the plasma concentration before dosing or at the end of the dosing interval of any dose

other than the first dose in a multiple dosing regimen. The analysis was done on the ITT population.

End point type	Secondary

End point timeframe:

Predose on Day 14 and Day 28

End point values	Panel 2: 90/400 mg LDV/SOF (Day 14)	Panel 2: SMV 150mg+LDV 90mg/SOF 400mg (Day 28)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	18[10]		
Units: ng/mL				
arithmetic mean (standard deviation)	376 (± 211)	659 (± 406)		

Notes:

[10] - Here 'N' signifies number of participants analysed for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach Maximum Plasma Concentration (Tmax) of LDV

End point title	Time to Reach Maximum Plasma Concentration (Tmax) of LDV

End point description:

The Tmax is defined as actual sampling time to reach maximum observed analyte concentration. The analysis was done on the ITT population.

End point type	Secondary

End point timeframe:

Predose, 0.5, 1, 2, 4, 6, 8, 10, 12, 18, and 24 hours postdose on Day 14 and Day 28

End point values	Panel 2: 90/400 mg LDV/SOF (Day 14)	Panel 2: SMV 150mg+LDV 90mg/SOF 400mg (Day 28)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	17[11]		
Units: hour				
median (full range (min-max))	4.07 (1 to 8)	6 (3.93 to 10)		

Notes:

[11] - Here 'N' signifies number of participants analysed for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Average Plasma Concentration at Steady State (Cavg,ss) of LDV

End point title	Average Plasma Concentration at Steady State (Cavg,ss) of LDV

End point description:

The Cavg,ss is calculated as area under the plasma concentration-time curve during a dosing Interval (AUC[tau]) divided by the dosing interval (tau). The analysis was done on the ITT population.

End point type	Secondary

End point timeframe:

Predose, 0.5, 1, 2, 4, 6, 8, 10, 12, 18, and 24 hours postdose on Day 14 and Day 28

End point values	Panel 2: 90/400 mg LDV/SOF (Day 14)	Panel 2: SMV 150mg+LDV 90mg/SOF 400mg (Day 28)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	17[12]		
Units: ng/mL				
arithmetic mean (standard deviation)	411 (± 207)	725 (± 364)		

Notes:

[12] - Here 'N' signifies number of participants analysed for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Fluctuation Index (FI) of LDV

End point title	Fluctuation Index (FI) of LDV

End point description:

Fluctuation index is defined as percentage fluctuation (variation between maximum and minimum concentration at steady state), calculated as: 100*([Cmax Cmin]/Cavg). The analysis was done on the ITT population.

End point type	Secondary

End point timeframe:

Predose, 0.5, 1, 2, 4, 6, 8, 10, 12, 18, and 24 hours postdose on Day 14 and Day 28

End point values	Panel 2: 90/400 mg LDV/SOF (Day 14)	Panel 2: SMV 150mg+LDV 90mg/SOF 400mg (Day 28)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	17[13]		
Units: percentage of fluctuation				
arithmetic mean (standard deviation)	60.6 (± 19.7)	51.2 (± 0.17)		

Notes:

[13] - Here 'N' signifies number of participants analysed for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of Participants With Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

An AE is any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. An SAE is an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. The analysis was done on the ITT population.

End point type	Secondary

End point timeframe:

Up to 10 Weeks for Panel 1 and 8 Weeks for Panel 2 (Treatment Phase)

End point values	Panel 1: SMV 150mg+LDV 90mg/SOF 400mg - 10 Weeks	Panel 2: SMV 150mg+LDV 90mg/SOF 400mg - 8 Weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: number of participants				
Adverse events	17	15		
Serious adverse events	2	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With On-treatment Virologic Response

End point title	Percentage of Participants With On-treatment Virologic Response

End point description:

On-treatment virologic response was determined by hepatitis C virus (HCV) ribonucleic acid (RNA) results satisfying a specified threshold.
The following thresholds were considered at any time point: less than (<)LLOQ undetectable, <LLOQ detectable and <LLOQ undetectable/detectable. The ITT analysis set is defined as all enrolled participants who took at least 1 dose of SMV, LDV, or SOF. The scheduled end of treatment visit for Panel 2 was Week 8. The analysis was done on the ITT population.

End point type	Secondary

End point timeframe:

Week 1, up to EOT (Week 10 in Panel 1 and Week 8 in Panel 2)

End point values	Panel 1: SMV 150mg+LDV 90mg/SOF 400mg - 10 Weeks	Panel 2: SMV 150mg+LDV 90mg/SOF 400mg - 8 Weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20[14]		
Units: percentage of participants				
number (not applicable)				
Week 1: >= 15 IU/mL	65	60		
Week 1: < 15 IU/mL undetectable/detectable	35	40		
Week 1: < 15 IU/mL detectable	15	35		
Week 1: < 15 IU/mL undetectable	20	5		
Week 2: >= 15 IU/mL	25	35		
Week 2: < 15 IU/mL undetectable/detectable	75	65		
Week 2: < 15 IU/mL detectable	30	30		
Week 2: < 15 IU/mL undetectable (vRVR)	45	35		
Week 4: >= 15 IU/mL	0	5		
Week 4: < 15 IU/mL undetectable/detectable	100	95		
Week 4: < 15 IU/mL detectable	15	5		
Week 4: < 15 IU/mL undetectable (RVR)	85	90		
Week 6: >= 15 IU/mL	0	0		
Week 6: < 15 IU/mL undetectable/detectable	100	100		
Week 6: < 15 IU/mL detectable	0	5		
Week 6: < 15 IU/mL undetectable	100	95		
Week 8: >= 15 IU/mL	0	0		
Week 8: < 15 IU/mL undetectable/detectable	100	100		
Week 8: < 15 IU/mL detectable	0	0		
Week 8: < 15 IU/mL undetectable	100	100		
Week 10: >= 15 IU/mL	0	999		
Week 10: < 15 IU/mL undetectable/detectable	100	999		
Week 10: < 15 IU/mL detectable	0	999		
Week 10: < 15 IU/mL undetectable	100	999		

Notes:

[14] - In Panel 2, 999 signifies "NA - Not Applicable" because Week 10 is not applicable for Panel 2.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Sustained Virologic Response (SVR) 4 Weeks After the Actual EOT (SVR4) and 12 Weeks After the Actual EOT (SVR12)

End point title	Percentage of Participants With Sustained Virologic Response (SVR) 4 Weeks After the Actual EOT (SVR4) and 12 Weeks After the Actual EOT (SVR12)

End point description:

SVR4 or SVR12 is defined as sustained virologic response 4 or 12 weeks after the actual EOT the participant has HCV RNA <LLOQ detectable or undetectable. The analysis was done on the ITT

population.

End point type	Secondary

End point timeframe:

4 weeks after EOT (Week 4 of follow-up phase in Panel 1 and Panel 2) and 12 weeks after EOT (Week 12 of follow-up phase in Panel 1 and Panel 2)

End point values	Panel 1: SMV 150mg+LDV 90mg/SOF 400mg - 10 Weeks	Panel 2: SMV 150mg+LDV 90mg/SOF 400mg - 8 Weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: percentage of participants				
number (not applicable)				
SVR4	100	100		
SVR12	100	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:

On-treatment failure is defined as participants who did not achieve SVR12 and with confirmed detectable HCV RNA at the actual end of treatment. This was to include participants with: 1) Viral breakthrough, defined as a confirmed increase of greater than (>)1 log10 in HCV RNA from nadir, or confirmed HCV RNA of >100 international units per Milliliters (IU/mL) in participants whose HCV RNA had previously been <LLOQ while on treatment; 2) Other with confirmed detectable HCV RNA at the actual end of treatment (example, completed, discontinued due to AEs, withdrawal of consent). The analysis was done on the ITT population.

End point type	Secondary

End point timeframe:

Day 70 in Panel 1 and Day 56 in Panel 2

End point values	Panel 1: SMV 150mg+LDV 90mg/SOF 400mg - 10 Weeks	Panel 2: SMV 150mg+LDV 90mg/SOF 400mg - 8 Weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: percentage of participants				
number (not applicable)	0	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 who did not achieve SVR12, with undetectable HCV RNA at the actual end of study drug treatment and confirmed HCV RNA greater than or equal to (>=) LLOQ during follow-up. The analysis was done on the ITT population.

End point type	Secondary

End point timeframe:

Up to Week 12 follow-up phase after EOT

End point values	Panel 1: SMV 150mg+LDV 90mg/SOF 400mg - 10 Weeks	Panel 2: SMV 150mg+LDV 90mg/SOF 400mg - 8 Weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: percentage of participants				
number (not applicable)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Not Achieving Sustained Virologic Response (SVR) Showing Emerging Mutation in HCV Nonstructural Protein 3/4A (NS3/4A), Nonstructural Protein 5A (NS5A), and Nonstructural Protein 5B (NS5B) Sequence

End point title	Number of Participants Not Achieving Sustained Virologic Response (SVR) Showing Emerging Mutation in HCV Nonstructural Protein 3/4A (NS3/4A), Nonstructural Protein 5A (NS5A), and Nonstructural Protein 5B (NS5B) Sequence

End point description:

The analysis was to be done on the ITT population. All the participants achieved SVR in the study, therefore the data was not collected for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, until end of follow-up phase (Week 12 of follow-up phase) in Panel 1 and Panel 2

End point values	Panel 1: SMV 150mg+LDV 90mg/SOF 400mg - 10 Weeks	Panel 2: SMV 150mg+LDV 90mg/SOF 400mg - 8 Weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[15]	0[16]		
Units: participants				
number (not applicable)				

Notes:

[15] - Data was not collected for this outcome measure.

[16] - Data was not collected for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 10 Weeks for Panel 1 and 8 Weeks for Panel 2 (Treatment Phase)

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Panel 1: SMV 150mg+LDV 90mg/SOF 400mg - 10 Wks

Reporting group description:

Participants received simeprevir (SMV) 150 milligram (mg) capsule and sofosbuvir (SOF) 400 mg tablet, orally, once daily from Day 1 until Day 14. From Day 15 until Day 70, participants received SMV 150 mg capsule and a fixed dose combination (FDC) tablet of 90 mg Ledipasvir (LDV)/400 mg SOF, orally and once daily.

Reporting group title	Panel 2: SMV 150mg+LDV 90mg/SOF 400mg - 8 Wks

Reporting group description:

Participants received FDC tablet of 90 mg LDV/400 mg SOF, orally, once daily from Day 1 until Day 14. From Day 15 until Day 56, participants received SMV 150 mg capsule and a FDC tablet of 90 mg LDV/400 mg SOF, orally and once daily.

Serious adverse events	Panel 1: SMV 150mg+LDV 90mg/SOF 400mg - 10 Wks	Panel 2: SMV 150mg+LDV 90mg/SOF 400mg - 8 Wks	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 20 (10.00%)	0 / 20 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Tibia fracture			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibula fracture			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (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	Panel 1: SMV 150mg+LDV 90mg/SOF 400mg - 10 Wks	Panel 2: SMV 150mg+LDV 90mg/SOF 400mg - 8 Wks	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 20 (85.00%)	15 / 20 (75.00%)	
Vascular disorders			
Hot flush			
subjects affected / exposed	2 / 20 (10.00%)	1 / 20 (5.00%)	
occurrences (all)	2	1	
Vasculitis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Catheter site paraesthesia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Asthenia			
subjects affected / exposed	2 / 20 (10.00%)	1 / 20 (5.00%)	
occurrences (all)	2	1	
Peripheral swelling			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	2 / 20 (10.00%)	1 / 20 (5.00%)	
occurrences (all)	2	1	
Pyrexia			
subjects affected / exposed	2 / 20 (10.00%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Reproductive system and breast disorders			
Breast atrophy			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 20 (10.00%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Psychiatric disorders			

Depression			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Insomnia			
subjects affected / exposed	1 / 20 (5.00%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	2 / 20 (10.00%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Headache			
subjects affected / exposed	1 / 20 (5.00%)	3 / 20 (15.00%)	
occurrences (all)	1	3	
Dizziness			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Disturbance in attention			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Presyncope			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Paraesthesia			
subjects affected / exposed	0 / 20 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Eye disorders			
Eye irritation			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Eyelid oedema			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Photophobia			

subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Vision blurred			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Constipation			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Abdominal pain upper			
subjects affected / exposed	2 / 20 (10.00%)	1 / 20 (5.00%)	
occurrences (all)	2	1	
Diarrhoea			
subjects affected / exposed	2 / 20 (10.00%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Dyspepsia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Flatulence			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	2 / 20 (10.00%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Hepatobiliary disorders			
Jaundice			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			

Alopecia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Erythema			
subjects affected / exposed	0 / 20 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Hyperhidrosis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Eczema			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Pruritus			
subjects affected / exposed	3 / 20 (15.00%)	3 / 20 (15.00%)	
occurrences (all)	3	3	
Photosensitivity reaction			
subjects affected / exposed	11 / 20 (55.00%)	7 / 20 (35.00%)	
occurrences (all)	17	12	
Purpura			
subjects affected / exposed	1 / 20 (5.00%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Rash			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 20 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Muscle spasms			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Angular cheilitis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Ear infection			

subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Genital abscess			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Laryngitis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Tooth infection			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Pneumonia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Oral herpes			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 May 2015	The amendment 1 included the following changes: prohibit the use of amiodarone from 60 days prior to screening until end of treatment (EOT) (instead of from screening onwards) to allow clearance of amiodarone plasma levels prior to initiation of treatment; include preliminary, in vitro data supporting an inhibitory potential of ledipasvir (LDV) on P-glycoprotein in the gut as well as hepatic organic anion transported protein 1B1/3; and a minor editorial change.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported