Clinical trial results:
A Phase 2b, Multicenter, Randomized, Open-label Study to Investigate the Efficacy, Safety and Pharmacokinetics of Different Treatment Regimens of AL-335, Odalasvir, and Simeprevir in Treatment-naive and Treatment-experienced Subjects With Chronic Hepatitis C Virus Genotype 1, 2, 4, 5 and 6 Infection Without Cirrhosis

Summary

EudraCT number	2015-004200-38
Trial protocol	DE BE PL IT
Global end of trial date	16 November 2017

Results information

Result version number	v1 (current)
This version publication date	31 October 2018
First version publication date	31 October 2018

Trial information

Trial identification

Sponsor protocol code	64294178HPC2001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02765490
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen-Cilag International NV
Sponsor organisation address	Turnhoutseweg 30, Beerse, Belgium, B-2340
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	16 November 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 November 2017
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 evaluate the efficacy, that is, the sustained virologic response 12 weeks (SVR) after the end of the treatment (EOT) (SVR12) of a combination treatment with AL-335, odalasvir (ODV), and simeprevir (SMV) for 6 and 8 weeks in chronic hepatitis C virus (HCV) genotype 1, 2, 4, 5 or 6 infected subjects without cirrhosis.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements. The safety assessments included Physical Examinations, Electrocardiograms (ECG's), Echocardiography, Vital Signs (pulse/heart rate and blood pressure) and Clinical Laboratory Tests.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 November 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 81
Country: Number of subjects enrolled	Canada: 63
Country: Number of subjects enrolled	Germany: 32
Country: Number of subjects enrolled	Spain: 58
Country: Number of subjects enrolled	Italy: 53
Country: Number of subjects enrolled	Poland: 61
Country: Number of subjects enrolled	Singapore: 17
Worldwide total number of subjects	365
EEA total number of subjects	285

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)	342
From 65 to 84 years	23
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 365 subjects (183 subjects in Arm A and 182 subjects in Arm B) were enrolled and treated in the study. Out of them 361 subjects (182 subjects in Arm A and 179 subjects in Arm B) completed the study.

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	Arm A: AL-335 800 mg+ODV 25 mg+SMV 75 mg qd for 6 Weeks

Arm description:

Subjects received AL-335 800 milligram (mg) (2*400) tablets, Odalasvir (ODV) 25 mg tablet, and Simeprevir (SMV) 75 mg capsule once daily (qd) orally in the morning for 6 weeks.

Arm type	Experimental
Investigational medicinal product name	AL-335
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received AL-335 800 mg (2*400) tablets qd in the morning for 6 weeks.

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

Dosage and administration details:

Subjects received Odalasvir 25 mg tablet qd in the morning for 6 weeks.

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

Dosage and administration details:

Subjects received Simeprevir 75 mg capsule qd in the morning for 6 weeks.

Arm title	Arm B: AL-335 800 mg+ODV 25 mg+SMV 75 mg qd for 8 Weeks

Arm description:

Subjects received AL-335 800 mg (2*400) tablets, Odalasvir 25 mg tablet, and Simeprevir 75 mg capsule qd orally in the morning for 8 weeks.

Arm type	Experimental

Investigational medicinal product name	AL-335
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received AL-335 800 mg (2*400) tablets qd in the morning for 8 weeks.

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

Dosage and administration details:

Subjects received Odalasvir 25 mg tablet qd in the morning for 8 weeks.

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

Dosage and administration details:

Subjects received Simeprevir 75 mg capsule qd in the morning for 8 weeks.

Number of subjects in period 1	Arm A: AL-335 800 mg+ODV 25 mg+SMV 75 mg qd for 6 Weeks	Arm B: AL-335 800 mg+ODV 25 mg+SMV 75 mg qd for 8 Weeks
Started	183	182
Completed	182	179
Not completed	1	3
Death	-	1
Lost to follow-up	1	2

Baseline characteristics

Reporting groups	
Reporting group title	Arm A: AL-335 800 mg+ODV 25 mg+SMV 75 mg qd for 6 Weeks
Reporting group description:	
Subjects received AL-335 800 milligram (mg) (2*400) tablets, Odalasvir (ODV) 25 mg tablet, and Simeprevir (SMV) 75 mg capsule once daily (qd) orally in the morning for 6 weeks.	
Reporting group title	Arm B: AL-335 800 mg+ODV 25 mg+SMV 75 mg qd for 8 Weeks
Reporting group description:	
Subjects received AL-335 800 mg (2*400) tablets, Odalasvir 25 mg tablet, and Simeprevir 75 mg capsule qd orally in the morning for 8 weeks.	

Reporting group values	Arm A: AL-335 800 mg+ODV 25 mg+SMV 75 mg qd for 6 Weeks	Arm B: AL-335 800 mg+ODV 25 mg+SMV 75 mg qd for 8 Weeks	Total
Number of subjects	183	182	365
Title for AgeCategorical			
Units: subjects			
Adults (18-64 years)	175	167	342
From 65 to 84 years	8	15	23
Title for AgeContinuous			
Units: years			
median	48	49	
full range (min-max)	19 to 69	18 to 70	-
Title for Gender			
Units: subjects			
Female	88	94	182
Male	95	88	183

End points

End points reporting groups

Reporting group title	Arm A: AL-335 800 mg+ODV 25 mg+SMV 75 mg qd for 6 Weeks
Reporting group description:	
Subjects received AL-335 800 milligram (mg) (2*400) tablets, Odalasvir (ODV) 25 mg tablet, and Simeprevir (SMV) 75 mg capsule once daily (qd) orally in the morning for 6 weeks.	
Reporting group title	Arm B: AL-335 800 mg+ODV 25 mg+SMV 75 mg qd for 8 Weeks
Reporting group description:	
Subjects received AL-335 800 mg (2*400) tablets, Odalasvir 25 mg tablet, and Simeprevir 75 mg capsule qd orally in the morning for 8 weeks.	

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

End point title	Percentage of Subjects With Sustained Virologic Response 12 Weeks after End of Treatment (EOT) (SVR12)[1]
End point description:	
The SVR 12 was defined as 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 subjects who took at least 1 dose of the study drug [that is AL-335, Odalasvir (ODV) or Simeprevir (SMV)].	
End point type	Primary
End point timeframe:	
Week 12 (Follow-Up Phase)	

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 this endpoint.

End point values	Arm A: AL-335 800 mg+ODV 25 mg+SMV 75 mg qd for 6 Weeks	Arm B: AL-335 800 mg+ODV 25 mg+SMV 75 mg qd for 8 Weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	183	182		
Units: Percentage of subjects				
number (confidence interval 95%)	98.9 (96.1 to 99.9)	97.8 (94.5 to 99.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Sustained Virologic Response 24 Weeks After End of Treatment (SVR24)

End point title	Percentage of Subjects With Sustained Virologic Response 24 Weeks After End of Treatment (SVR24)

End point description:

The SVR24 was defined as HCV RNA <LLOQ (detectable or undetectable) 24 weeks after End of Treatment (EOT). ITT population included all randomized subjects who took at least 1 dose of the study drug (i.e., AL-335, ODV or SMV). Last Observation Carried Forward (LOCF) method was used to impute the missing values.

End point type	Secondary

End point timeframe:

Week 24 (Follow-Up Phase)

End point values	Arm A: AL-335 800 mg+ODV 25 mg+SMV 75 mg qd for 6 Weeks	Arm B: AL-335 800 mg+ODV 25 mg+SMV 75 mg qd for 8 Weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	183	182		
Units: Percentage of subjects				
number (confidence interval 95%)	98.9 (96.1 to 99.9)	97.3 (93.7 to 99.1)		

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:

Viral Relapse: Subjects who did not achieve SVR12, with HCV RNA <LLOQ at the EOT and confirmed HCV RNA greater than or equal to (>=) LLOQ during follow-up. ITT population included all randomized subjects who took at least 1 dose of the study drug (i.e., AL-335, ODV or SMV).

End point type	Secondary

End point timeframe:

End of Treatment up to Week 24 (Follow up phase)

End point values	Arm A: AL-335 800 mg+ODV 25 mg+SMV 75 mg qd for 6 Weeks	Arm B: AL-335 800 mg+ODV 25 mg+SMV 75 mg qd for 8 Weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	183	182		
Units: Subjects	1	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Late Viral Relapse

End point title	Number of Subjects With Late Viral Relapse

End point description:

Late Viral Relapse: Subjects who achieved SVR12 but had confirmed HCV RNA >=LLOQ afterwards during follow-up. ITT population included all randomized subjects who took at least 1 dose of the study drug (i.e., AL-335, ODV or SMV).

End point type	Secondary

End point timeframe:

Up to Week 24 (Follow-up Phase)

End point values	Arm A: AL-335 800 mg+ODV 25 mg+SMV 75 mg qd for 6 Weeks	Arm B: AL-335 800 mg+ODV 25 mg+SMV 75 mg qd for 8 Weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	183	182		
Units: Subjects	0	1		

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:

On-treatment failure: Subjects who did not achieve SVR12 and with confirmed HCV RNA>=LLOQ at the End of Treatment (EOT). ITT population included all randomized subjects who took at least 1 dose of the study drug (i.e., AL-335, ODV or SMV).

End point type	Secondary

End point timeframe:

EOT up to Week 12 (Follow up Phase)

End point values	Arm A: AL-335 800 mg+ODV 25 mg+SMV 75 mg qd for 6 Weeks	Arm B: AL-335 800 mg+ODV 25 mg+SMV 75 mg qd for 8 Weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	183	182		
Units: Percentage of subjects				
number (not applicable)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Sustained Virologic Response 4 Weeks after End of Treatment (EOT)

End point title	Percentage of Subjects With Sustained Virologic Response 4 Weeks after End of Treatment (EOT)

End point description:

The SVR 4 was defined as subjects who were considered to reach SVR4, if 4 weeks after the actual EOT, HCV RNA was <LLOQ (detectable or undetectable). ITT population included all randomized subjects who took at least 1 dose of the study drug (i.e., AL-335, ODV or SMV).

End point type	Secondary

End point timeframe:

Week 4 (Follow-Up Phase)

End point values	Arm A: AL-335 800 mg+ODV 25 mg+SMV 75 mg qd for 6 Weeks	Arm B: AL-335 800 mg+ODV 25 mg+SMV 75 mg qd for 8 Weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	183	182		
Units: Percentage of subjects				
number (confidence interval 95%)	99.5 (97.0 to 100.0)	98.4 (95.3 to 99.7)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Screening up to Follow-up (Week 24)	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups	
Reporting group title	Arm A: AL-335 800 mg+ODV 25 mg+SMV 75 mg qd for 6 Weeks
Reporting group description:	
Subjects received AL-335 800 milligram (mg) (2*400) tablets, Odalasvir (ODV) 25 mg tablet, and Simeprevir (SMV) 75 mg capsule once daily (qd) orally in the morning for 6 weeks.	
Reporting group title	Arm B: AL-335 800 mg+ODV 25 mg+SMV 75 mg qd for 8 Weeks
Reporting group description:	
Subjects received AL-335 800 mg (2*400) tablets, Odalasvir 25 mg tablet, and Simeprevir 75 mg capsule qd orally in the morning for 8 weeks.	

Serious adverse events	Arm A: AL-335 800 mg+ODV 25 mg+SMV 75 mg qd for 6 Weeks	Arm B: AL-335 800 mg+ODV 25 mg+SMV 75 mg qd for 8 Weeks	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 183 (3.83%)	4 / 182 (2.20%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign Breast Neoplasm			
subjects affected / exposed	0 / 183 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glioblastoma			
subjects affected / exposed	0 / 183 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
Hypertension			

subjects affected / exposed	1 / 183 (0.55%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
IVth Nerve Paresis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parkinsonism			
subjects affected / exposed	0 / 183 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Intestinal Obstruction			
subjects affected / exposed	1 / 183 (0.55%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal Strangulation			
subjects affected / exposed	1 / 183 (0.55%)	0 / 182 (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			
subjects affected / exposed	1 / 183 (0.55%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Choking			
subjects affected / exposed	1 / 183 (0.55%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back Pain			

subjects affected / exposed	1 / 183 (0.55%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infective Keratitis			
subjects affected / exposed	0 / 183 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower Respiratory Tract Infection			
subjects affected / exposed	0 / 183 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm A: AL-335 800 mg+ODV 25 mg+SMV 75 mg qd for 6 Weeks	Arm B: AL-335 800 mg+ODV 25 mg+SMV 75 mg qd for 8 Weeks	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	83 / 183 (45.36%)	85 / 182 (46.70%)	
Nervous system disorders			
Headache			
subjects affected / exposed	40 / 183 (21.86%)	40 / 182 (21.98%)	
occurrences (all)	63	49	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	11 / 183 (6.01%)	8 / 182 (4.40%)	
occurrences (all)	11	9	
Fatigue			
subjects affected / exposed	27 / 183 (14.75%)	21 / 182 (11.54%)	
occurrences (all)	30	22	
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	7 / 183 (3.83%)	10 / 182 (5.49%)	
occurrences (all)	8	13	
Nausea			
subjects affected / exposed	13 / 183 (7.10%)	5 / 182 (2.75%)	
occurrences (all)	16	5	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	15 / 183 (8.20%)	15 / 182 (8.24%)	
occurrences (all)	16	16	
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	8 / 183 (4.37%)	12 / 182 (6.59%)	
occurrences (all)	9	13	
Myalgia			
subjects affected / exposed	10 / 183 (5.46%)	13 / 182 (7.14%)	
occurrences (all)	12	17	
Infections and infestations			
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	13 / 183 (7.10%)	19 / 182 (10.44%)	
occurrences (all)	15	21	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 June 2016	The overall reason for the amendment is to change in design of the Phase 2b study with focus on evaluating the 3 Direct-Acting Antiviral Agent (DAA) treatment regimen comprising of AL-335+Odalasvir (ODV) with Simeprevir (SMV).
12 August 2016	The overall reason for the amendment is to change in design of the Phase 2b study with focus on treatment-naive and treatment-experienced hepatitis C virus (HCV) genotype 1, 2, 4, 5 or 6 infected subjects without cirrhosis.
10 April 2017	The overall reason for the amendment is to implement study treatment stopping rules upon Health Authority feedback. In addition, as more subjects have been recruited than originally planned for, the actual number of subjects enrolled in the study is added and statistical considerations for safety are adjusted accordingly.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported