



## Clinical trial results:

**An Open-Label, Single-Arm Phase III Study to Evaluate the Efficacy, Safety and Tolerability of TMC435 in Combination With PegIFN alfa-2a (Pegasys) and Ribavirin (Copegus) in Treatment-Naive or Treatment-Experienced, Chronic Hepatitis C Virus Genotype-4 Infected participants.**

### Summary

EudraCT number	2011-004097-29
Trial protocol	BE
Global end of trial date	20 March 2014

### Results information

Result version number	v1
This version publication date	06 July 2016
First version publication date	20 June 2015

### Trial information

#### Trial identification

Sponsor protocol code	TMC435HPC3011
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01567735
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	Janssen R&D Ireland
Sponsor organisation address	Eastgate Village, Eastgate, Little Island, Co. Cork, Ireland,
Public contact	Clinical Registry Group, Janssen Research & Development, +353 21 4673500, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Janssen Research & Development, +353 21 4673500, 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	20 March 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	20 March 2014
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The primary objective is to evaluate the efficacy of TMC435 in combination with PegIFN $\alpha$ -2a/RBV with respect to the proportion of participants with chronic HCV-4 infection achieving SVR 12 weeks after planned end of treatment (SVR12) in the overall population as well as in the different subpopulations (treatment-naïve, previous relapsers and previous nonresponders).

Protection of trial subjects:

Safety and tolerability were evaluated throughout the study by monitoring of adverse events (AEs), performing laboratory tests, monitoring of adverse events (AEs), measurement of vital signs, electrocardiogram and performing physical examinations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 February 2012
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: 38
Country: Number of subjects enrolled	France: 69
Worldwide total number of subjects	107
EEA total number of subjects	107

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)	100
From 65 to 84 years	7

85 years and over	0
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## Subject disposition

### Recruitment

Recruitment details:

The study was conducted from 16 February 2012 to 20 March 2014.

### Pre-assignment

Screening details:

136 participants were screened of whom 107 participants were treated and 103 participants completed the study.

### Period 1

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

### Arms

Arm title	simeprevir (TMC435)
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Arm description:

Participants received TMC435 150 mg once daily plus peginterferon alfa-2a (PegIFN alfa-2a) and ribavirin (RBV) for 12 Weeks (Wks) followed by PegIFN alfa-2a (P) and RBV (R) until Week 24/48 (PR24/48). Treatment was to be stopped at Week 24 for HCV treatment-naïve and prior HCV relapsers who met the response guided therapy criteria. All prior HCV non-responders (null and partial), and HCV treatment-naïve and prior HCV relapsers who did not meet the response guided therapy criteria had a 48-week treatment period.

Arm type	Experimental
Investigational medicinal product name	simeprevir
Investigational medicinal product code	TMC435
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants received TMC435 150 mg once daily plus peginterferon alfa-2a (PegIFN alfa-2a) and ribavirin (RBV) for 12 Weeks (Wks) followed by PegIFN alfa-2a (P) and RBV (R) until Week 24/48 (PR24/48). Treatment was to be stopped at Week 24 for HCV treatment-naïve and prior HCV relapsers who met the response guided therapy criteria. All prior HCV non-responders (null and partial), and HCV treatment-naïve and prior HCV relapsers who did not meet the response guided therapy criteria had a 48-week treatment period.

Number of subjects in period 1	simeprevir (TMC435)
Started	107
Completed	103
Not completed	4
Consent withdrawn by subject	1
Lost to follow-up	3

## Baseline characteristics

### Reporting groups

Reporting group title	simeprevir (TMC435)
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Reporting group description:

Participants received TMC435 150 mg once daily plus peginterferon alfa-2a (PegIFN alfa-2a) and ribavirin (RBV) for 12 Weeks (Wks) followed by PegIFN alfa-2a (P) and RBV (R) until Week 24/48 (PR24/48). Treatment was to be stopped at Week 24 for HCV treatment-naïve and prior HCV relapsers who met the response guided therapy criteria. All prior HCV non-responders (null and partial), and HCV treatment-naïve and prior HCV relapsers who did not meet the response guided therapy criteria had a 48-week treatment period.

Reporting group values	simeprevir (TMC435)	Total	
Number of subjects	107	107	
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	100	100	
From 65 to 84 years	7	7	
85 years and over	0	0	
Title for AgeContinuous Units: years			
median	49		
full range (min-max)	27 to 69	-	
Title for Gender Units: subjects			
Female	23	23	
Male	84	84	

## End points

### End points reporting groups

Reporting group title	simeprevir (TMC435)
Reporting group description: Participants received TMC435 150 mg once daily plus peginterferon alfa-2a (PegIFN alfa-2a) and ribavirin (RBV) for 12 Weeks (Wks) followed by PegIFN alfa-2a (P) and RBV (R) until Week 24/48 (PR24/48). Treatment was to be stopped at Week 24 for HCV treatment-naïve and prior HCV relapsers who met the response guided therapy criteria. All prior HCV non-responders (null and partial), and HCV treatment-naïve and prior HCV relapsers who did not meet the response guided therapy criteria had a 48-week treatment period.	
Subject analysis set title	Intent-to-treat (ITT) population
Subject analysis set type	Intention-to-treat
Subject analysis set description: Intent-to-treat (ITT) population, which includes all participants who took at least 1 dose of study medication.	

### Primary: Percentage of participants achieving sustained virologic response 12 weeks after planned end of treatment (SVR12)

End point title	Percentage of participants achieving sustained virologic response 12 weeks after planned end of treatment (SVR12) <sup>[1]</sup>
End point description: Participants are considered to have reached SVR12 if both conditions below are met: 1) HCV RNA levels less than (<) 25 International unit per milliliter (IU/mL) undetectable at the actual end of treatment; 2) HCV RNA levels <25 IU/mL undetectable or HCV RNA levels <25 IU/mL detectable 12 weeks after planned end of treatment. SVR 12 was reported for overall population (that is, ITT population), treatment naïve, relapser and non-responder participants. 'N' (number of participants analyzed) signifies the participants evaluable for this measure and "n" signifies those participants who were evaluated for this measure at the specified time point.	
End point type	Primary
End point timeframe: 12 Weeks After the Planned End of Treatment (Planned EOT: if participant eligible for response-guided treatment (RGT) and met the criteria: Week 24; otherwise Week 48)	

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: Statistical analysis was not reported for this endpoint as inferential analysis was not performed as planned.

End point values	simeprevir (TMC435)			
Subject group type	Reporting group			
Number of subjects analysed	107 <sup>[2]</sup>			
Units: Percentage of participants				
number (not applicable)				
Overall SVR12 (n=107)	65.4			
Treatment naïve (n=35)	82.9			
Relapser(n=22)	86.4			
Non-Responder(n=50)	44			

Notes:

[2] - ITT Population

### Statistical analyses

No statistical analyses for this end point

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**Secondary: Percentage of participants achieving sustained virologic response 4 weeks after planned end of treatment (SVR4)**

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End point title	Percentage of participants achieving sustained virologic response 4 weeks after planned end of treatment (SVR4)
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End point description:

Participants are considered to have reached SVR4 and SVR 12 if both conditions below are met: 1) HCV RNA levels less than <25 International unit per milliliter (IU/mL) undetectable (at the actual end of treatment);2) HCV RNA levels <25 IU/mL undetectable or HCV RNA levels <25 IU/mL detectable (4, 12, 24, 36 and 48 weeks after the planned EOT).

End point type	Secondary
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End point timeframe:

4 weeks after Planned EOT (if participant eligible for response-guided treatment (RGT) and met the criteria: Week 24; otherwise Week 48)

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End point values	simeprevir (TMC435)			
Subject group type	Reporting group			
Number of subjects analysed	107 <sup>[3]</sup>			
Units: Percentage of Participants				
number (not applicable)	68.2			

Notes:

[3] - ITT Population

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Percentage of participants achieving sustained virologic response 24 weeks after planned end of treatment (SVR24).**

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End point title	Percentage of participants achieving sustained virologic response 24 weeks after planned end of treatment (SVR24).
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End point description:

Participants are considered to have reached SVR24 if both conditions below are met: 1) HCV RNA levels less than <25 International units per milliliter (IU/mL) undetectable (at the actual end of treatment);2) HCV RNA levels <25 IU/mL undetectable or HCV RNA levels <25 IU/mL detectable (24 weeks after the planned EOT).

End point type	Secondary
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End point timeframe:

24 Weeks After the Planned EOT (if participant eligible for response-guided treatment (RGT) and met the criteria: Week 24; otherwise Week 48)

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<b>End point values</b>	simeprevir (TMC435)			
Subject group type	Reporting group			
Number of subjects analysed	107 <sup>[4]</sup>			
Units: Percentage of participants				
number (not applicable)	65.4			

Notes:

[4] - ITT Population

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants With On-treatment Virologic Failure

End point title	Percentage of Participants With On-treatment Virologic Failure
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End point description:

Participants were considered as an on-treatment failure if, at actual end of treatment (EOT), there was confirmed detectable HCV RNA levels.

End point type	Secondary
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End point timeframe:

Actual EOT (Week 24 or Week 48 or Early withdrawal)

<b>End point values</b>	simeprevir (TMC435)			
Subject group type	Reporting group			
Number of subjects analysed	107 <sup>[5]</sup>			
Units: percentage of participants				
number (not applicable)	23.4			

Notes:

[5] - ITT Population

## 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
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End point description:

Viral breakthrough was defined as a confirmed increase of more than 1 log<sub>10</sub> in Hepatitis C Virus (HCV) ribonucleic acid (RNA) level from the lowest level reached or a confirmed value of HCV RNA more than 100 international units/milliliter (IU/mL) in participants whose HCV RNA was previously less than 25 IU/mL.

End point type	Secondary
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End point timeframe:

Up to Actual EOT (Week 24 or Week 48 or Early withdrawal)



<b>End point values</b>	simeprevir (TMC435)			
Subject group type	Reporting group			
Number of subjects analysed	107 <sup>[6]</sup>			
Units: percentage of participants				
number (not applicable)	18.7			

Notes:

[6] - ITT Population

## 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
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End point description:

Participants are considered to have a viral relapse if both conditions as specified are met: 1) <25 IU/mL undetectable HCV RNA at the actual end of study drug treatment; 2) confirmed HCV RNA greater than or equal to ( $\geq$ ) 25 IU/mL during follow-up. 'N' (number of participants analyzed) signifies those participants who were evaluable for this measure. The incidence of viral relapse is only calculated for subjects with undetectable HCV RNA levels (or unconfirmed detectable) at EOT and with at least one follow-up HCV RNA measurement.

End point type	Secondary
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End point timeframe:

Actual EOT (Week 24 or Week 48 or Early withdrawal) upto end of follow up period

<b>End point values</b>	simeprevir (TMC435)			
Subject group type	Reporting group			
Number of subjects analysed	82			
Units: percentage of participants				
number (not applicable)	14.6			

## 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)
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End point description:

An AE was any untoward medical event that occurs in a participant administered an investigational product, and it does not necessarily indicate only events with clear causal relationship with the relevant investigational product. An SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged in-patient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly.

End point type	Secondary
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End point timeframe:

Upto End of treatment (EOT:week 48)

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<b>End point values</b>	simeprevir (TMC435)			
Subject group type	Reporting group			
Number of subjects analysed	107 <sup>[7]</sup>			
Units: Participants				
number (not applicable)				
AEs	104			
SAEs	8			

Notes:

[7] - ITT Population

### Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Baseline up to End of Treatment (EOT: Week 24 or Week 48 or Early Withdrawal)

Adverse event reporting additional description:

Adverse events were reported for the entire treatment phase.

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	14.1
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### Reporting groups

Reporting group title	Simeprevir(TMC435)
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Reporting group description:

Participants received TMC435 150 mg once daily plus peginterferon alfa-2a (PegIFN alfa-2a) and ribavirin (RBV) for 12 Weeks (Wks) followed by PegIFN alfa-2a (P) and RBV (R) until Week 24/48 (PR24/48). Treatment was to be stopped at Week 24 for HCV treatment-naïve and prior HCV relapsers who met the response guided therapy criteria. All prior HCV non-responders (null and partial), and HCV treatment-naïve and prior HCV relapsers who did not meet the response guided therapy criteria had a 48-week treatment period.

Serious adverse events	Simeprevir(TMC435)		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 107 (7.48%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bradycardia			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Nervous system disorders			
Headache			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spondylitic myelopathy			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haematemesis			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diabetes mellitus			

subjects affected / exposed	2 / 107 (1.87%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

<b>Non-serious adverse events</b>	Simeprevir(TMC435)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	104 / 107 (97.20%)		
Nervous system disorders			
Headache			
subjects affected / exposed	28 / 107 (26.17%)		
occurrences (all)	34		
Dizziness			
subjects affected / exposed	6 / 107 (5.61%)		
occurrences (all)	7		
General disorders and administration site conditions			
Chills			
subjects affected / exposed	6 / 107 (5.61%)		
occurrences (all)	6		
Influenza like illness			
subjects affected / exposed	51 / 107 (47.66%)		
occurrences (all)	56		
Asthenia			
subjects affected / exposed	49 / 107 (45.79%)		
occurrences (all)	62		
Fatigue			
subjects affected / exposed	38 / 107 (35.51%)		
occurrences (all)	63		
Injection site erythema			
subjects affected / exposed	6 / 107 (5.61%)		
occurrences (all)	6		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	18 / 107 (16.82%)		
occurrences (all)	21		

Leukopenia subjects affected / exposed occurrences (all)	6 / 107 (5.61%) 7		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	11 / 107 (10.28%) 11		
Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all)  Dry mouth subjects affected / exposed occurrences (all)  Constipation subjects affected / exposed occurrences (all)  Nausea subjects affected / exposed occurrences (all)  Diarrhoea subjects affected / exposed occurrences (all)	9 / 107 (8.41%) 9  6 / 107 (5.61%) 6  8 / 107 (7.48%) 8  11 / 107 (10.28%) 13  13 / 107 (12.15%) 15		
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)  Epistaxis subjects affected / exposed occurrences (all)  Cough subjects affected / exposed occurrences (all)	20 / 107 (18.69%) 20  6 / 107 (5.61%) 7  23 / 107 (21.50%) 26		
Skin and subcutaneous tissue disorders Pruritus			

subjects affected / exposed	32 / 107 (29.91%)		
occurrences (all)	34		
Rash			
subjects affected / exposed	13 / 107 (12.15%)		
occurrences (all)	16		
Dry skin			
subjects affected / exposed	28 / 107 (26.17%)		
occurrences (all)	32		
Alopecia			
subjects affected / exposed	9 / 107 (8.41%)		
occurrences (all)	9		
Erythema			
subjects affected / exposed	9 / 107 (8.41%)		
occurrences (all)	12		
Skin lesion			
subjects affected / exposed	6 / 107 (5.61%)		
occurrences (all)	6		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	24 / 107 (22.43%)		
occurrences (all)	26		
Depression			
subjects affected / exposed	9 / 107 (8.41%)		
occurrences (all)	14		
Mood altered			
subjects affected / exposed	13 / 107 (12.15%)		
occurrences (all)	16		
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	12 / 107 (11.21%)		
occurrences (all)	12		
Arthralgia			
subjects affected / exposed	6 / 107 (5.61%)		
occurrences (all)	6		
Back pain			

subjects affected / exposed occurrences (all)	10 / 107 (9.35%) 11		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	7 / 107 (6.54%) 7		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	22 / 107 (20.56%) 25		



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 February 2012	Based on consultations with Health Authorities, the following substantial changes: The definitions for SVR12 and SVR24 were evaluated and updated and it clarified that a liver biopsy is the required method for all subjects without a contraindication for this procedure.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported