



## Clinical trial results:

### A Prospective 3-year Follow-up Study in Subjects Previously Treated in a Phase IIb or Phase III Study with a TMC435-containing Regimen for the Treatment of Hepatitis C Virus (HCV) Infection

#### Summary

EudraCT number	2010-019843-20
Trial protocol	DE PL
Global end of trial date	05 January 2016

#### Results information

Result version number	v1 (current)
This version publication date	12 January 2017
First version publication date	12 January 2017

#### Trial information

##### Trial identification

Sponsor protocol code	TMC435HPC3002
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01349465
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Janssen Research & Development, a division of Janssen Pharmaceutica NV
Sponsor organisation address	Turnhoutseweg 30, Beerse, Belgium, 2340
Public contact	Clinical Registry Group, Janssen-Cilag International, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Janssen-Cilag International, 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	05 January 2016
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	05 January 2016
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The Main objective of the study was to evaluate the durability of sustained virologic response (SVR) in subjects who were treated with a simeprevir (SMV)-containing regimen in a previous Phase 2b or Phase 3 study and maintained undetectable hepatitis C virus (HCV) ribonucleic acid (RNA) until the last post-therapy follow-up visit of the previous study (LPVPS) and to evaluate sequence changes in the HCV NS3/4A region over time in subjects who were treated with a SMV-containing regimen in a previous Phase 2b or Phase 3 study and had confirmed detectable HCV RNA at LPVPS.

Protection of trial subjects:

The safety assessments included laboratory assessments (hematology, serum chemistry, and Coagulation), and Adverse events were monitored throughout the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 July 2011
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: 27
Country: Number of subjects enrolled	Canada: 32
Country: Number of subjects enrolled	Germany: 49
Country: Number of subjects enrolled	France: 24
Country: Number of subjects enrolled	Poland: 29
Country: Number of subjects enrolled	Russian Federation: 45
Country: Number of subjects enrolled	United States: 43
Worldwide total number of subjects	249
EEA total number of subjects	129

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)	237
From 65 to 84 years	12
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

In total 250 subjects were screened and among those 249 were enrolled into the study (200 subjects with SVR and 49 subjects with no SVR).

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	SVR at LPVPS

Arm description:

Subjects with sustained virologic response (SVR) at last posttherapy visit of the previous study (LPVPS).

Arm type	Follow up Phase (Simeprevir)
Investigational medicinal product name	Simeprevir
Investigational medicinal product code	
Other name	TMC 435
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Subjects did not receive any treatment during this study and this is the follow up phase for Simeprevir.

<b>Arm title</b>	no SVR at LPVPS
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Arm description:

Subjects with no sustained virologic response (SVR) at last posttherapy visit of the previous study (LPVPS).

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	SVR at LPVPS	no SVR at LPVPS
Started	200	49
Completed	182	27
Not completed	18	22
Adverse event, serious fatal	3	-
Consent withdrawn by subject	4	2
Adverse event	1	-
Lost to follow-up	10	1
Subject ineligible to continue the trial	-	19



## Baseline characteristics

### Reporting groups

Reporting group title	SVR at LPVPS
Reporting group description: Subjects with sustained virologic response (SVR) at last posttherapy visit of the previous study (LPVPS).	
Reporting group title	no SVR at LPVPS
Reporting group description: Subjects with no sustained virologic response (SVR) at last posttherapy visit of the previous study (LPVPS).	

Reporting group values	SVR at LPVPS	no SVR at LPVPS	Total
Number of subjects	200	49	249
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	193	44	237
From 65 to 84 years	7	5	12
85 years and over	0	0	0
Title for AgeContinuous Units: years			
median	52	56	
full range (min-max)	22 to 70	28 to 70	-
Title for Gender Units: subjects			
Female	78	17	95
Male	122	32	154

## End points

### End points reporting groups

Reporting group title	SVR at LPVPS
Reporting group description:	
Subjects with sustained virologic response (SVR) at last posttherapy visit of the previous study (LPVPS).	
Reporting group title	no SVR at LPVPS
Reporting group description:	
Subjects with no sustained virologic response (SVR) at last posttherapy visit of the previous study (LPVPS).	

### Primary: Percentage of Subjects Maintaining SVR at the Last Available Visit

End point title	Percentage of Subjects Maintaining SVR at the Last Available Visit <sup>[1][2]</sup>
End point description:	
The SVR rate is the proportion (%) of subjects with HCV RNA less than (<) 25 International Units/milliliter (IU/mL).	
End point type	Primary
End point timeframe:	
Last Available Visit (Month 36 for subjects completing the study)	

#### 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 statistics were done, no inferential statistical analyses were performed.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The data represented only for with SVR LPVPS.

<b>End point values</b>	SVR at LPVPS			
Subject group type	Reporting group			
Number of subjects analysed	200			
Units: Percentage of subjects				
number (confidence interval 95%)	100 (98.2 to 100)			

### Statistical analyses

No statistical analyses for this end point

### Primary: Overall Percentage of Subjects With Change in Sequence of HCV NS3/4A Region Over Time in Subjects With Confirmed Detectable HCV RNA at the Last Visit of the Previous Study

End point title	Overall Percentage of Subjects With Change in Sequence of HCV NS3/4A Region Over Time in Subjects With Confirmed Detectable HCV RNA at the Last Visit of the Previous Study <sup>[3][4]</sup>
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#### End point description:

Sequencing was performed to assess changes in the sequence of the HCV NS3/4A protein region over time in subjects with no SVR at LPVPS (ie confirmed detectable HCV RNA at the last visit of the previous study). EOS defined as last available sequencing sample. AEM and NEM represents any emerging

mutation and no emerging mutation at time of failure of the previous study. "N" signifies number of subjects with no SVR at LPVPS and with available sequence data. "n" defines the number of subjects analyzed at specified time point.

End point type	Primary
End point timeframe:	
Baseline and Month 36	

Notes:

[3] - 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 statistics were done, no inferential statistical analyses were performed.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	no SVR at LPVPS			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: Percentage of subjects				
number (not applicable)				
NEM Return to Baseline at EOS (n=5)	0			
NEM Change to New Profile at EOS (n=5)	0			
AEM Return to Baseline at EOS (n=43)	86			
AEM Change to New Profile at EOS (n=43)	7			

## Statistical analyses

No statistical analyses for this end point

### Primary: Percentage of Subjects With Change in Sequence of HCV NS3/4A Region Over Time in Subjects With Confirmed Detectable HCV RNA (With Q80K at baseline) at the Last Visit of the Previous Study

End point title	Percentage of Subjects With Change in Sequence of HCV NS3/4A Region Over Time in Subjects With Confirmed Detectable HCV RNA (With Q80K at baseline) at the Last Visit of the Previous Study <sup>[5][6]</sup>
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End point description:

Sequencing was performed to assess changes in the sequence of the HCV NS3/4A protein region over time in subjects with no SVR at LPVPS (ie confirmed detectable HCV RNA at the last visit of the previous study). EOS defined as last available sequencing sample. AEM and NEM represents any emerging mutation and no emerging mutation at time of failure of the previous study. Subjects with no SVR at LPVPS were included in the population analysis set. "N" signifies the number of available subjects with sequence data and "n" defines the number of subjects analyzed at specified time point.

End point type	Primary
End point timeframe:	
Baseline and Month 36	

Notes:

[5] - 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 statistics were done, no inferential statistical analyses were performed.

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The data represented only for with noSVR LPVPS.



End point values	no SVR at LPVPS			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: Percentage of subjects				
number (not applicable)				
NEM Return to Baseline at EOS (n=1)	0			
NEM Change to New Profile at EOS (n=1)	0			
AEM Return to Baseline at EOS (n=9)	88.9			
AEM Change to New Profile at EOS (n=9)	0			

## Statistical analyses

No statistical analyses for this end point

### Primary: Percentage of Subjects With Change in Sequence of HCV NS3/4A Region Over Time in Subjects With Confirmed Detectable HCV RNA (Without Q80K at baseline) at the Last Visit of the Previous Study

End point title	Percentage of Subjects With Change in Sequence of HCV NS3/4A Region Over Time in Subjects With Confirmed Detectable HCV RNA (Without Q80K at baseline) at the Last Visit of the Previous Study <sup>[7][8]</sup>
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End point description:

Sequencing was performed to assess changes in the sequence of the HCV NS3/4A protein region over time in subjects with no SVR at LPVPS (ie confirmed detectable HCV RNA at the last visit of the previous study). EOS defined as last available sequencing sample. AEM and NEM represents any emerging mutation and no emerging mutation at time of failure of the previous study. Subjects with no SVR at LPVPS were included in the population analysis set. "N" signifies the number of available subjects with sequence data and "n" defines the number of subjects analyzed at specified time point.

End point type	Primary
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End point timeframe:

Baseline and Month 36

Notes:

[7] - 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 statistics were done, no inferential statistical analyses were performed.

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	no SVR at LPVPS			
Subject group type	Reporting group			
Number of subjects analysed	38			
Units: Percentage of subjects				
number (not applicable)				
NEM Return to Baseline at EOS (n=4)	0			
NEM Change to New Profile at EOS (n=4)	0			
AEM Return to Baseline at EOS (n=34)	85.3			
AEM Change to New Profile at EOS (n=34)	8.8			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects With Late Viral Relapse

End point title	Percentage of Subjects With Late Viral Relapse <sup>[9]</sup>
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End point description:

Relapse at any time after the LPVPS until the last individual visit of this study. All subjects maintained SVR until the last available visit. No late viral relapse was therefore observed. Late viral relapse was evaluated in all enrolled subjects with SVR at LPVPS.

End point type	Secondary
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End point timeframe:

End of study (at month 36)

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The data represented only for with SVR LPVPS.

End point values	SVR at LPVPS			
Subject group type	Reporting group			
Number of subjects analysed	200			
Units: Percentage of subjects				
number (not applicable)	0			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects with Adverse Events (AEs) as a Measure of Safety and Tolerability

End point title	Number of Subjects with Adverse Events (AEs) as a Measure of Safety and Tolerability
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End point description:

End point type	Secondary
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End point timeframe:

End of study (at month 36)

<b>End point values</b>	SVR at LPVPS	no SVR at LPVPS		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	200	49		
Units: subjects				
Adverse Events (AE)	4	1		
Serious Adverse Events (SAE)	10	0		

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

End of study (36 Months)

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	SVR at LPVPS
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Reporting group description:

Subjects with SVR at LPVPS

Reporting group title	no SVR at LPVPS
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Reporting group description:

Subjects with No SVR at LPVPS

Reporting group title	Total
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Reporting group description:

All enrolled subjects in the study.

Serious adverse events	SVR at LPVPS	no SVR at LPVPS	Total
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 200 (5.00%)	0 / 49 (0.00%)	10 / 249 (4.02%)
number of deaths (all causes)	3	0	3
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatic neoplasm malignant			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 200 (1.50%)	0 / 49 (0.00%)	3 / 249 (1.20%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Colon cancer			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 200 (0.50%)	0 / 49 (0.00%)	1 / 249 (0.40%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal tract adenoma			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 200 (0.50%)	0 / 49 (0.00%)	1 / 249 (0.40%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic carcinoma			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 200 (0.50%)	0 / 49 (0.00%)	1 / 249 (0.40%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Cardiac disorders			
Myocardial infarction			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 200 (0.50%)	0 / 49 (0.00%)	1 / 249 (0.40%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Nervous system disorders			
Cerebrovascular accident			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 200 (0.50%)	0 / 49 (0.00%)	1 / 249 (0.40%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 200 (0.50%)	0 / 49 (0.00%)	1 / 249 (0.40%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 200 (0.50%)	0 / 49 (0.00%)	1 / 249 (0.40%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain upper			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 200 (0.50%)	0 / 49 (0.00%)	1 / 249 (0.40%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 200 (0.50%)	0 / 49 (0.00%)	1 / 249 (0.40%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 200 (0.50%)	0 / 49 (0.00%)	1 / 249 (0.40%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 200 (0.50%)	0 / 49 (0.00%)	1 / 249 (0.40%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 200 (0.50%)	0 / 49 (0.00%)	1 / 249 (0.40%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varices oesophageal			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 200 (0.50%)	0 / 49 (0.00%)	1 / 249 (0.40%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Biliary colic			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 200 (0.50%)	0 / 49 (0.00%)	1 / 249 (0.40%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 200 (0.50%)	0 / 49 (0.00%)	1 / 249 (0.40%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hydrocholecystis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 200 (0.50%)	0 / 49 (0.00%)	1 / 249 (0.40%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

<b>Non-serious adverse events</b>	SVR at LPVPS	no SVR at LPVPS	Total
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 200 (2.00%)	1 / 49 (2.04%)	5 / 249 (2.01%)
Investigations			
Alpha 1 foetoprotein increased			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 200 (0.00%)	1 / 49 (2.04%)	1 / 249 (0.40%)
occurrences (all)	0	1	1
Nervous system disorders			
Dysarthria			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 200 (0.50%)	0 / 49 (0.00%)	1 / 249 (0.40%)
occurrences (all)	1	0	1
Hemiparesis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 200 (0.50%)	0 / 49 (0.00%)	1 / 249 (0.40%)
occurrences (all)	1	0	1
Blood and lymphatic system disorders			

Iron deficiency anaemia alternative assessment type: Systematic subjects affected / exposed occurrences (all)	1 / 200 (0.50%) 1	0 / 49 (0.00%) 0	1 / 249 (0.40%) 1
Hepatobiliary disorders Bile duct stone alternative assessment type: Systematic subjects affected / exposed occurrences (all)	1 / 200 (0.50%) 1	0 / 49 (0.00%) 0	1 / 249 (0.40%) 1
Cholecystitis chronic alternative assessment type: Systematic subjects affected / exposed occurrences (all)	1 / 200 (0.50%) 1	0 / 49 (0.00%) 0	1 / 249 (0.40%) 1



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 January 2011	The main purpose of this amendment was to extended the follow-up period from 1 to 3 years, also added clinical endpoints (eg, liver disease progression).

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported