Clinical trial results:
A Phase 3, Open-label Trial of TMC435 in Combination With Peginterferon -2a and Ribavirin for HCV Genotype 1 Infected Subjects who Participated in the Placebo Group of a Phase 2/3 TMC435 Study (C201, C205, C206, C208, C216 or HPC3007), or who Received Short-term (up to 14 Days) Direct-acting Antiviral Treatment for Hepatitis C Infection in a Selected Tibotec*-sponsored Phase 1 Study

Summary

EudraCT number	2011-000416-25
Trial protocol	BE GB ES AT PT NL DE PL BG
Global end of trial date	31 March 2015

Results information

Result version number	v1 (current)
This version publication date	19 March 2016
First version publication date	19 March 2016

Trial information

Trial identification

Sponsor protocol code	TMC435-TiDP16-C213

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01323244
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen R&D Ireland
Sponsor organisation address	Eastgate Village, Little island, Co. Cork, Ireland,
Public contact	Janssen R&D Ireland, Janssen R&D Ireland, ClinicalTrialsEU@its.jnj.com
Scientific contact	Janssen R&D Ireland, Janssen R&D Ireland, ClinicalTrialsEU@its.jnj.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 March 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 March 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the efficacy of SMV (Simeprevir) in combination with PegIFNα-2a and RBV (Ribavirin), with respect to the proportion of subjects with SVR12 (Sustained virologic response 12).

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 study protocol was reviewed by an Independent Ethics Committee. Safety evaluations were based upon the type, incidence, and severity of AEs (adverse events) reported throughout the study, changes in clinical laboratory tests (hematology, biochemistry and urinalysis), vital sign measurements, 12-lead ECGs (electrocardiogram), physical examination (including weight, height, and temperature), and monitoring of hypoglycemia.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 December 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	Israel: 3
Country: Number of subjects enrolled	Argentina: 2
Country: Number of subjects enrolled	Australia: 7
Country: Number of subjects enrolled	Austria: 6
Country: Number of subjects enrolled	Belgium: 9
Country: Number of subjects enrolled	Bulgaria: 1
Country: Number of subjects enrolled	Brazil: 3
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	Germany: 13
Country: Number of subjects enrolled	Spain: 7
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Mexico: 1
Country: Number of subjects enrolled	Netherlands: 10
Country: Number of subjects enrolled	New Zealand: 2
Country: Number of subjects enrolled	Poland: 18

Country: Number of subjects enrolled	Portugal: 4
Country: Number of subjects enrolled	Romania: 2
Country: Number of subjects enrolled	Russian Federation: 16
Country: Number of subjects enrolled	Ukraine: 5
Country: Number of subjects enrolled	United States: 20
Worldwide total number of subjects	141
EEA total number of subjects	79

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)	131
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Total 141 participants were enrolled in this study; who had participated in the placebo group of a Phase 2/3 SMV study, or who had received short-term (up to 14 days) DAA treatment for HCV infection in the selected JRDsponsored Phase 1 studies.

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 150mg 12Wks PR24/48

Arm description:

In the first 24 weeks, subjects received SMV (simeprevir) 150 milligram (mg) daily in combination with PegIFNá 2a [peginterferon alfa-2a (Pegasys) 180 microgram] and RBV [ribavirin (Copegus)] for 12 weeks, followed by
12 weeks of PegIFNá 2a and RBV or 48 weeks.

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:

In the first 24 weeks, subjects received SMV (simeprevir) 150 milligram (mg) daily in combination with PegIFNα 2a [peginterferon alfa-2a (Pegasys)] and RBV [ribavirin (Copegus)] for 12 weeks, followed by 12 weeks of PegIFNα 2a and RBV or 48 weeks.

Investigational medicinal product name	Peginterferon alfa-2a (PegIFNα-2a)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

PegIFNα-2a was given as Pegasys 180 mc (microgram) once a week, administered as subcutaneous (SC) injection of 0.5 mL (millilitre) for 24 weeks or 48 weeks.

Investigational medicinal product name	Ribavirin (RBV)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

If the baseline body weight was more than <75 kg (kilogram), the total daily dose of Ribavarin (RBV) was 1,000 (mg) milligram, administered as 400 mg (2 tablets of 200 mg) in the morning and 600 mg (3 tablets of 200 mg) in the evening. If the baseline body weight was less than or equal to ≥75 kg, the total daily dose was 1,200 mg, administered as 2 x 600 mg (3 tablets of 200 mg per intake, morning and evening).

Number of subjects in period 1	Simeprevir 150mg 12Wks PR24/48
Started	141
Completed	127
Not completed	14
Consent withdrawn by subject	8
Lost to follow-up	6

Baseline characteristics

Reporting groups	
Reporting group title	Simeprevir 150mg 12Wks PR24/48
Reporting group description:	
In the first 24 weeks, subjects received SMV (simeprevir) 150 milligram (mg) daily in combination with PegIFNá 2a [peginterferon alfa-2a (Pegasys) 180 microgram] and RBV [ribavirin (Copegus)] for 12 weeks, followed by 12 weeks of PegIFNá 2a and RBV or 48 weeks.	

Reporting group values	Simeprevir 150mg 12Wks PR24/48	Total	
Number of subjects	141	141	
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	131	131	
From 65 to 84 years	10	10	
85 years and over	0	0	
Title for AgeContinuous Units: years			
median	52		
full range (min-max)	22 to 72	-	
Title for Gender Units: subjects			
Female	48	48	
Male	93	93	

End points

End points reporting groups

Reporting group title	Simeprevir 150mg 12Wks PR24/48

Reporting group description:

In the first 24 weeks, subjects received SMV (simeprevir) 150 milligram (mg) daily in combination with PegIFNá 2a [peginterferon alfa-2a (Pegasys) 180 microgram] and RBV [ribavirin (Copegus)] for 12 weeks, followed by
12 weeks of PegIFNá 2a and RBV or 48 weeks.

Subject analysis set title	Phase 2/3 Group
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects who had participated in the Placebo group of Phase 2/3 SMV (sustained virologic response) study and subjects with HCV genotype 1 infection who had received short-term (up to 14 days) DAA (direct-acting antiviral agent) treatment for HCV (hepatitis C virus) infection in Phase 1 study.

Subject analysis set title	Phase 1 Group
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects who had participated in the Placebo group of Phase 2/3 SMV (Sustained virologic response) study and subjects with HCV genotype 1 infection who had received short-term (up to 14 days) DAA (direct-acting antiviral agent) treatment for HCV (hepatitis C virus) infection in Phase 1 study.

Primary: The percentage of participants with sustained viral response at 12 weeks after the planned End of Treatment (SVR12)

End point title	The percentage of participants with sustained viral response at 12 weeks after the planned End of Treatment (SVR12)[1]

End point description:

Subjects were considered to have achieved SVR 12 if 2 conditions were met: 1) at the actual end of treatment - HCV RNA <25 IU/mL undetectable, and 2) 12 weeks after the planned EOT - HCV RNA <25 IU/mL undetectable or detectable.Intend to treat population included all randomized participants who received at least 1 dose of the study drug.

End point type	Primary

End point timeframe:

12 Weeks After the Planned End of Treatment

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: No statistical analysis has been performed for this endpoint.

End point values	Phase 2/3 Group	Phase 1 Group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	125	16		
Units: Percentage				
number (confidence interval 95%)	69.6 (61.5 to 77.7)	37.5 (13.8 to 61.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: The percentage of participants with sustained viral response at 4 and 24

weeks after planned end of treatment (SVR4 and SVR24)

End point title	The percentage of participants with sustained viral response at 4 and 24 weeks after planned end of treatment (SVR4 and SVR24)

End point description:

Subjects were considered to have achieved SVR X if 2 conditions were met: 1) at the actual end of treatment - HCV RNA <25 IU/mL undetectable, and 2) X weeks after the planned EOT - HCV RNA <25 IU/mL undetectable or detectable. Intend to treat population included all randomized participants who received at least 1 dose of the study drug.

End point type	Secondary

End point timeframe:

24 weeks after planned end of treatment

End point values	Phase 2/3 Group	Phase 1 Group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	125	16		
Units: Percentage				
number (confidence interval 95%)				
Sustained virologic response 4 weeks (SVR4)	73.6 (65.9 to 81.3)	37.5 (13.8 to 61.2)		
Sustained virologic response 24 weeks (SVR24)	69.6 (61.5 to 77.7)	37.5 (13.8 to 61.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline of 'on-treatment' HCV RNA level

End point title	Change from baseline of 'on-treatment' HCV RNA level

End point description:

Intend to treat population included all randomized participants who received at least 1 dose of the study drug.

End point type	Secondary

End point timeframe:

On treatment

End point values	Phase 2/3 Group	Phase 1 Group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	125[2]	16[3]		
Units: Log10 International Unit per milliliter				
arithmetic mean (standard error)				
Week 1 (n=122, 15)	-4.47 (± 0.06)	-4.36 (± 0.14)		
Week 4 (n=125, 15)	-5.17 (± 0.09)	-5.47 (± 0.09)		
Week 8 (n=118, 15)	-5.36 (± 0.09)	-5.63 (± 0.11)		

Notes:

[2] - N signifies number of subjects for this endpoints

[3] - N signifies number of subjects for this endpoints

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with viral breakthrough

End point title	Number of participants with viral breakthrough

End point description:

Viral breakthrough was defined as a confirmed increase of more than >1 log10 IU/mL (International Unit per millilitre) in HCV RNA level from the lowest level reached, or a confirmed HCV Hepatitis C Virus RNA level of more than >100 IU/mL in subjects whose HCV RNA levels had previously been below the limit of quantification (less than <25 IU/mL detectable) or undetectable (<25 IU/mL undetectable) while on study treatment. Intend to treat population included all randomized participants who received at least 1 dose of the study drug.

End point type	Secondary

End point timeframe:

Up to End of treatment

End point values	Phase 2/3 Group	Phase 1 Group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	125	15		
Units: Percentage				
number (not applicable)	9.6	6.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with viral relapse

End point title	Number of participants with viral relapse

End point description:

Viral relapse was defined as undetectable HCV RNA at the actual end of treatment and HCV RNA measurement during follow-up more than or equal to ≥25 IU/mL (International unit per millilitre). The incidence of viral relapse was only calculated for subjects with undetectable HCV RNA at end of treatment and with at least 1 follow up HCV RNA measurement.Intend to treat population included all randomized participants who received at least 1 dose of the study drug.

End point type	Secondary

End point timeframe:

Through Week 48

End point values	Phase 2/3 Group	Phase 1 Group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	104	12		
Units: Percentage				
number (not applicable)	14.4	41.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with 'on-treatment' normalized alanine aminotransferase levels

End point title	Number of participants with 'on-treatment' normalized alanine aminotransferase levels

End point description:

Intend to treat population included all randomized participants who received at least 1 dose of the study drug.

End point type	Secondary

End point timeframe:

End of treatment

End point values	Phase 2/3 Group	Phase 1 Group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	59	6		
Units: Percentage				
number (not applicable)				
No Normalization	28.8	16.7		
Normalization	71.2	83.3		

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:

Subjects were considered as an on-treatment failure if: at actual EOT (End of treatment), detectable HCV RNA levels (ie, Less than 25 IU/mL (International unit per milliliter) detectable or =>25 IU/mL) were noted. Intend to treat population included all randomized participants who received at least 1 dose of the study drug.

End point type	Secondary

End point timeframe:

End of treatment

End point values	Phase 2/3 Group	Phase 1 Group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	125	16		
Units: Percentage				
number (not applicable)	16	18.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants affected by an adverse event

End point title	Number of participants affected by an adverse event

End point description:

An adverse event (AE) is defined as any untoward medical occurrence in a participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. A serious adverse event (SAE) is defined as any untoward medical occurrence that, at any dose: results in death; is life-threatening; requires hospitalization or prolongation of existing hospitalization; results in disability/incapacity; or is a congenital anomaly/birth defect. Medical or scientific judgment should have been exercised in other situations. Refer to the general AE/SAE module for a list of AEs (occurring at a frequency threshold >=3%) and SAEs. Intend to treat population included all randomized participants who received at least 1 dose of the study drug.

End point type	Secondary

End point timeframe:

End of treatment

End point values	Simeprevir 150mg 12Wks PR24/48			
Subject group type	Reporting group			
Number of subjects analysed	141			
Units: Percentage				
number (not applicable)				
Simeprevir + PR Phase	90.8			
Entire Treatment Phase	92.9			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Entire Treatment Phase

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups

Reporting group title	Simeprevir 150mg 12Wks PR24/48

Reporting group description:

Participants in this study will receive TMC435 in combination with peginterferon alfa-2a (Pegasys) and ribavirin (Copegus) followed by peginterferon alfa-2a and ribavirin alone. The total treatment duration will be 24 or 48 weeks, depending on how the patients respond to treatment and which was their previous response to peginterferon alfa-2a and ribavirin alone. After a patient stops taking study medication, subjects receiving a planned 24 weeks of treatment continue in the trial until Week 48, while subjects receiving a planned 48 weeks of treatment continue in the trial until Week 72.The total duration of the study is 78 weeks (including screening).The above arm description is for subjects from a Phase II/III group trial. Subjects from a Phase I group trial were also included, these subjects had a planned treatment duration of 48 weeks, followed by 24 weeks of Follow-up.

Serious adverse events	Simeprevir 150mg 12Wks PR24/48		
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 141 (6.38%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Renal cell carcinoma			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Clavicle fracture			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hand fracture			

subjects affected / exposed	1 / 141 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Procedural pain			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Pancytopenia			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Papilloedema			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Biloma			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchitis			

subjects affected / exposed	1 / 141 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Erysipelas			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Simeprevir 150mg 12Wks PR24/48		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	127 / 141 (90.07%)		
Nervous system disorders			
Headache			
subjects affected / exposed	32 / 141 (22.70%)		
occurrences (all)	40		
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	31 / 141 (21.99%)		
occurrences (all)	35		
Fatigue			
subjects affected / exposed	52 / 141 (36.88%)		
occurrences (all)	59		
Asthenia			
subjects affected / exposed	18 / 141 (12.77%)		
occurrences (all)	19		
Pyrexia			
subjects affected / exposed	24 / 141 (17.02%)		
occurrences (all)	81		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	35 / 141 (24.82%)		
occurrences (all)	78		
Anaemia			

subjects affected / exposed occurrences (all)	20 / 141 (14.18%) 24		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all)	 11 / 141 (7.80%) 12 26 / 141 (18.44%) 29 10 / 141 (7.09%) 10 10 / 141 (7.09%) 12 8 / 141 (5.67%) 10		
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all)	 13 / 141 (9.22%) 13 11 / 141 (7.80%) 12		
Hepatobiliary disorders Hyperbilirubinaemia subjects affected / exposed occurrences (all)	 14 / 141 (9.93%) 23		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all)	 25 / 141 (17.73%) 30 26 / 141 (18.44%) 33		

Dry skin subjects affected / exposed occurrences (all) Alopecia subjects affected / exposed occurrences (all)	 11 / 141 (7.80%) 11 14 / 141 (9.93%) 14		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) Mood altered subjects affected / exposed occurrences (all) Depression subjects affected / exposed occurrences (all)	 23 / 141 (16.31%) 26 9 / 141 (6.38%) 9 15 / 141 (10.64%) 17		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all)	 12 / 141 (8.51%) 12 20 / 141 (14.18%) 26		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	 17 / 141 (12.06%) 18		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 January 2012	There were 3 substantial and 2 non-substantial amendments to the original protocol, dated 26 May 2011. In addition, there were 4 country-specific amendments for Israel. The second general protocol amendment, dated 10 January 2012, was considered substantial and was based on feedback from the Health Authorities. A strong correlation between SVR12 and SVR24 was demonstrated in completed SMV Phase 2b studies (C205 and C206), and in telaprevir and boceprevir Phase 3 studies. Health Authorities agreed that the primary efficacy endpoint for ongoing and future SMV Phase 3 studies could be changed from SVR24 to SVR12. SVR24 became a secondary endpoint. It was clarified that the thyroid function of the subjects should be adequately controlled and that subjects with abnormal thyroid-stimulating hormone (TSH) levels would be excluded from the study or should stop treatment. The antinuclear antibody (ANA) titer and TSH levels were added to exclusion criterion 10. Specific management of pancreatic amylase or lipase elevations, gastrointestinal nausea (with or without vomiting) and diarrhea were deleted from the specific toxicities section and general guidelines on management of graded AEs and laboratory abnormalities considered at least possibly related to SMV. The platelet and absolute neutrophil count in exclusion criteria 13 was revised to facilitate enrollment of African American subjects in the study. It was clarified that the Roche Cobas TaqMan HCV Test v2.0, for use with the High Pure System was used as the assay to determine HCV RNA levels. The performance characteristics of the assay reported by the manufacturer as well as the internal assay performance validation document were added to the reference list. A liver biopsy inclusion criterion was added to the protocol. A liver biopsy was the required method for all subjects without a contraindication for this procedure.
18 April 2013	The protocol was amended to update the RGT duration criteria and the treatment stopping rules based on the Phase 3 results. Virologic stopping rules were modified so that subjects with HCV RNA ?25 IU/mL at Week 4 discontinued all treatment. Indeed, results from Phase 3 studies showed that the best predictor of achieving SVR with SMV plus PegIFN/RBV therapy is the Week 4 response, which is therefore considered an optimal and early time point for a decision regarding continuing or discontinuing therapy with the objective to terminize unnecessary exposure to treatment in subjects with very low likelihood of achieving SVR. Total treatment duration rules in eligible subjects (ie, subjects with viral relapse or breakthrough during prior PegIFN/RBV therapy in the control arm of SMV Phase 2/3 studies) were modified in line with the observations from Phase 3 studies, so that only subjects with undetectable HCV RNA at Week 4 and 12 could complete all treatment at Week 24, whereas subjects with HCV RNA <25 IU/mL detectable at Week 4 and undetectable at Week 12 were to receive 48 weeks of PegIFN?-2a/RBV treatment. The stopping rule at Week 12 was adapted: Subjects with detectable HCV RNA at Week 12 discontinued all treatment in line with analysis from the Phase 2b C206 study in prior nonresponders and Phase 3 studies in treatment naïve and prior relapse subjects, showing that subjects not achieving undetectable HCV RNA at Week 12 had a very low chance of achieving SVR. This modified stopping rule (ie, confirmed detectable HCV RNA) was also applicable at Week 24 and Week 36. The management of laboratory abnormalities and management of specific toxicities was updated and clarified based on the results from Phase 3 studies. It was determined that it was not necessary to discontinue study medication for isolated grade 4 abnormalities in bilirubin.

17 September 2013	It includes phase 1 photosensitivity study C125 had concluded that the photosensitizing potential of SMV is similar to that of placebo. Accordingly, formal recommendations for sun protective measures were removed from the ongoing SMV studies at the time that these results became available, and not included in future SMV study protocols. After analysis of the Phase 3 (C208/C216/HPC3007) studies, in which subjects were dosed with SMV prior to removal of recommendation for sun-protective measures, photosensitivity conditions were nevertheless identified as adverse drug reaction of SMV as detailed in the updated IB edition 7, issued in June 2013.34 As a follow-up to a recommendation by the United States (US) Food and Drug Administration (FDA), it was decided to reintroduce the same recommendations initially included in Phase 3 studies (C208/C216/HPC3007), in SMV studies where subjects were still being dosed with SMV and in any future SMV study. Therefore, the protocol was amended to reintroduce the precautionary language on photosensitivity.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The low sample size in the Phase 1 group was considered a study limitation by the sponsor.

Notes: