Clinical trial results:
An Open, Multicentre, Phase IV Study, Evaluating the Effect of a Drop In Hemoglobin Level on the Rate of Sustained Virologic Response In Chronic Hepatitis C Patients Treated With Ribavirin (Copegus®) in Combination With Standard Treatment (ANECO)

Summary

EudraCT number	2011-001256-10
Trial protocol	CZ
Global end of trial date	22 January 2014

Results information

Result version number	v1 (current)
This version publication date	14 July 2016
First version publication date	06 August 2015

Trial information

Trial identification

Sponsor protocol code	ML25186

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01585324
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.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	22 January 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 January 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this clinical study was the determination of a possible coincidence between the drop in hemoglobin concentration and the number of achieved sustained virologic response (SVR) in participants with chronic hepatitis C, infected by genotype 1, treated with ribavirin (Copegus®) in a combination with standard treatment of chronic hepatitis C (peginterferon alpha-2a).

Protection of trial subjects:

The clinical study was performed in accordance with ICH-GCP and Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 January 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	Czech Republic: 30
Worldwide total number of subjects	30
EEA total number of subjects	30

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)	30
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This clinical trial was originally planned in 4 clinical trial centers in the Czech Republic. However, due to a failure in manufacturing of the drug Pegasys, three of the previously approved study centers withdrew from participation. Consequently the sponsor decided to conduct the clinical trial in one of the four originally planned centers.

Period 1

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

Arms

Arm title	Peginterferon Alpha-2a + Ribavirin

Arm description:

Participants infected with hepatitis C virus (HCV) genotype 1, who were either treatment naïve or failed to respond to previous combination therapy with interferon and ribavirin, were included in the study. These participants were treated with a combination therapy of peginterferon alpha-2a injection at a dose of 180 micrograms (mcg) subcutaneously once a week and ribavirin tablet, 1000-1200 milligrams (mg) by body weight (1000 mg if weight less than [<] 75 kilogram [kg]; 1200 mg if weight greater than or equal to [≥] 75 kg) orally split into 2 daily divided doses, for a total of 48 weeks .

Arm type	Experimental
Investigational medicinal product name	Ribavirin
Investigational medicinal product code	
Other name	Copegus
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Ribavirin 1000-1200 mg by body weight (1000 mg if weight <75 kg; 1200 mg if weight ≥75 kg) tablet orally once daily in 2 divided doses, for a total of 48 weeks.

Investigational medicinal product name	Peginterferon alpha-2a
Investigational medicinal product code	
Other name	Pegasys
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Peginterferon alpha-2a at a dose of 180 mcg subcutaneously once a week, for a total of 48 weeks.

Number of subjects in period 1	Peginterferon Alpha-2a + Ribavirin
Started	30
Completed	30

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study Period
Reporting group description:	
All participants who received at least 1 dose of study drug were included.	

Reporting group values	Overall Study Period	Total	
Number of subjects	30	30	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	32.1		
standard deviation	± 7.2	-	
Gender categorical Units: Subjects			
Female	1	1	
Male	29	29	

End points

End points reporting groups

Reporting group title	Peginterferon Alpha-2a + Ribavirin

Reporting group description:

Participants infected with hepatitis C virus (HCV) genotype 1, who were either treatment naïve or failed to respond to previous combination therapy with interferon and ribavirin, were included in the study. These participants were treated with a combination therapy of peginterferon alpha-2a injection at a dose of 180 micrograms (mcg) subcutaneously once a week and ribavirin tablet, 1000-1200 milligrams (mg) by body weight (1000 mg if weight less than [<] 75 kilogram [kg]; 1200 mg if weight greater than or equal to [≥] 75 kg) orally split into 2 daily divided doses, for a total of 48 weeks .

Subject analysis set title	Participants With SVR
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Included all participants infected with HCV genotype 1, who were either treatment naïve or failed to respond to previous combination therapy with interferon and ribavirin, but achieved SVR after treatment with a combination therapy of peginterferon alpha-2a at a dose of 180 mcg subcutaneously once a week and ribavirin 1000-1200 mg by body weight (1000 mg if weight <75 kg; 1200 mg if weight ≥75 kg) orally once daily in 2 divided doses, for a total of 48 weeks. SVR response was defined as a disappearance of HCV viral load 24 weeks after the end of the treatment.

Subject analysis set title	Participants Without SVR
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Included all participants infected with HCV genotype 1, who were either treatment naïve or failed to respond to previous combination therapy with interferon and ribavirin, and did not achieve SVR after treatment with a combination therapy of peginterferon alpha-2a at a dose of 180 mcg subcutaneously once a week and ribavirin 1000-1200 mg by body weight (1000 mg if weight <75 kg; 1200 mg if weight ≥75 kg) orally once daily in 2 divided doses, for a total of 48 weeks. SVR response was defined as a disappearance of HCV viral load 24 weeks after the end of the treatment.

Primary: Percentage of Participants With SVR 24 Weeks After end of Treatment

End point title	Percentage of Participants With SVR 24 Weeks After end of Treatment[1]

End point description:

SVR was defined as a disappearance of HCV viral load 24 weeks after the end of the treatment. Intention-to-treat (ITT) Population defined as all enrolled participants who received at least 1 dose of study drug.

End point type	Primary

End point timeframe:

24 weeks after the end of treatment (72 weeks)

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: Due to EudraCT limitation, it is not possible to provide statistical analysis for single arm.

End point values	Peginterferon Alpha-2a + Ribavirin			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: percentage of participants				
number (confidence interval 95%)	83.3 (65.28 to 94.36)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Hemoglobin Level at Week 12 of Treatment Among Participants With or Without SVR

End point title	Change From Baseline in Hemoglobin Level at Week 12 of Treatment Among Participants With or Without SVR[2]

End point description:

ITT Population.

End point type	Primary

End point timeframe:

Baseline and Week 12

Notes:

[2] - 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 was planned for this endpoint.

End point values	Participants With SVR	Participants Without SVR		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25	5		
Units: grams per liter (g/L)				
arithmetic mean (standard deviation)	-23 (± 14.768)	-32.4 (± 11.502)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Decrease in Hemoglobin

End point title	Number of Participants With Decrease in Hemoglobin

End point description:

The drop in Hb level at Week 12 compared to level at baseline was assessed and categorized in pre-defined categories (up to 20, 20-40, >40 g/L) for the group of participants who achieved SVR and in the group of participants without SVR. ITT Population.

End point type	Secondary

End point timeframe:

Week 12

End point values	Participants With SVR	Participants Without SVR		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25	5		
Units: Participants				
Up to 20 g/L	9	0		
20-40 g/L	14	3		
>40 g/L	2	2		

Statistical analyses

Statistical analysis title	Number of Participants With Decrease in Hemoglobin
Comparison groups	Participants With SVR v Participants Without SVR
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0867
Method	Fisher exact

Secondary: Lowest Hemoglobin Level During Treatment Among Participants With or Without SVR

End point title	Lowest Hemoglobin Level During Treatment Among Participants With or Without SVR

End point description:

The mean minimum hemoglobin value achieved during the treatment was assessed in the group of participants who achieved SVR and in the group of participants without SVR. ITT Population.

End point type	Secondary

End point timeframe:

Week 12

End point values	Participants With SVR	Participants Without SVR		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25	5		
Units: g/L				
arithmetic mean (standard deviation)	124.24 (± 10.08)	126.6 (± 10.383)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Reduction in Ribavirin Dose Due to Drop in Hemoglobin Among Participants With or Without SVR

End point title	Number of Participants With Reduction in Ribavirin Dose Due to Drop in Hemoglobin Among Participants With or Without SVR

End point description:

Number of participants with reduction in ribavirin dose due to decrease in Hb level was assessed in the group of participants who achieved SVR and in the group of participants without SVR. ITT Population.

End point type	Secondary
End point timeframe: Week 12	

End point values	Participants With SVR	Participants Without SVR		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25	5		
Units: Participants	1	0		

Statistical analyses

Statistical analysis title	Participants With Reduction in Ribavirin Dose
Comparison groups	Participants Without SVR v Participants With SVR
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6492
Method	ANCOVA

Secondary: Number of Participants With Neutropenia Among Participants With or Without SVR

End point title	Number of Participants With Neutropenia Among Participants With or Without SVR
End point description: ITT Population.	
End point type	Secondary
End point timeframe: Week 12	

End point values	Participants With SVR	Participants Without SVR		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25	5		
Units: participants	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Thrombocytopenia Among Participants With or Without SVR

End point title	Number of Participants With Thrombocytopenia Among Participants With or Without SVR
End point description: ITT Population.	
End point type	Secondary
End point timeframe: Week 12	

End point values	Participants With SVR	Participants Without SVR		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25	5		
Units: participants	1	0		

Statistical analyses

Statistical analysis title	Participants With Thrombocytopenia by SVR Status
Comparison groups	Participants With SVR v Participants Without SVR
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0333
Method	Wilcoxon (Mann-Whitney)

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From baseline up to 24 weeks after end of treatment (up to 72 weeks)	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups	
Reporting group title	peginterferon alpha-2a + Ribavirin

Reporting group description:

Participants infected with HCV genotype 1, who were either treatment naïve or failed to respond to previous combination therapy with interferon and ribavirin, were included in the study. These participants were treated with a combination therapy of peginterferon alpha-2a at a dose of 180 mcg subcutaneously once a week and ribavirin 1000-1200 mg by body weight (1000 mg if weight <75 kg; 1200 mg if weight >=75 kg) orally once daily in 2 divided doses, for a total of 48 weeks.

Serious adverse events	peginterferon alpha-2a + Ribavirin		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 30 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

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

Non-serious adverse events	peginterferon alpha-2a + Ribavirin		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 30 (63.33%)		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	5 / 30 (16.67%)		
occurrences (all)	38		
influenza like illness			
subjects affected / exposed	14 / 30 (46.67%)		
occurrences (all)	20		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported