Clinical trial results:
A Phase IIb, Open Label, Single Arm, Multicenter Study to Evaluate the Effect of 48-weeks Peginterferon alfa-2a (PEG-IFN) Administration on Serum HBsAg in Chronic Hepatitis B, HBeAg-Negative, Genotype D Patients on Treatment with Nucleos(t)ide Analogues (NAs), Showing Stable HBV DNA Suppression.

Summary

EudraCT number	2012-000080-25
Trial protocol	IT
Global end of trial date	25 November 2014

Results information

Result version number	v1
This version publication date	10 July 2016
First version publication date	10 July 2016

Trial information

Trial identification

Sponsor protocol code	ML28262

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01706575
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	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, 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	Interim
Date of interim/final analysis	18 December 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 September 2013
Global end of trial reached?	Yes
Global end of trial date	25 November 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the decline in serum Hepatitis B surface Antigen (HBsAg) at the end of combination treatment with Pegylated Interferon (Peginterferon) Alfa-2a (PEG-IFN) and nucleos(t)ide analogues (NA) (Study Week 48).

Protection of trial subjects:

All study subjects were required to read and sign an informed consent form.

Background therapy:

Subjects continued to nucleos(t)ide analogues (NA) therapy along with the study medication.

Evidence for comparator: -

Actual start date of recruitment	24 January 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	11 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 76
Worldwide total number of subjects	76
EEA total number of subjects	76

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)	76
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 76 subjects started the study and were included in lead-in period. Out of 76 subjects, 70 received study drug. Data is reported here for the interim analysis (up to 48 weeks).

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	Pegylated Interferon (Peginterferon) Alfa-2a

Arm description:

Subjects receiving nucleos(t)ide analogues (NA) therapy with Hepatitis B surface Antigen (HBsAg) decline less than (<) 0.5 log 10 international unit/milliliter (IU/ml) at baseline received peginterferon alfa-2a 180 microgram (mcg), subcutaneously (SC) once weekly for 48 weeks along with their NA therapy.

Arm type	Experimental
Investigational medicinal product name	Pegylated Interferon (Peginterferon) Alfa-2a
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Peginterferon alfa-2a 180 mcg, subcutaneously (SC) once weekly for 48 weeks.

Number of subjects in period 1	Pegylated Interferon (Peginterferon) Alfa-2a
Started	76
Completed	46
Not completed	30
Lack of Compliance	1
Started but not Treated	6
Subject Withdrew Consent	2
Adverse Event	8
No HBsAg Decrease at Week 24	11
Reason not Specified	2

Baseline characteristics

Reporting groups	
Reporting group title	Pegylated Interferon (Peginterferon) Alfa-2a

Reporting group description:

Subjects receiving nucleos(t)ide analogues (NA) therapy with Hepatitis B surface Antigen (HBsAg) decline less than (<) 0.5 log 10 international unit/milliliter (IU/ml) at baseline received peginterferon alfa-2a 180 microgram (mcg), subcutaneously (SC) once weekly for 48 weeks along with their NA therapy.

Reporting group values	Pegylated Interferon (Peginterferon) Alfa-2a	Total	
Number of subjects	76	76	
Age categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean	30.98		
standard deviation	± 12.33	-	
Gender categorical Units: Subjects			
Female	13	13	
Male	63	63	

End points

End points reporting groups

Reporting group title	Pegylated Interferon (Peginterferon) Alfa-2a

Reporting group description:

Subjects receiving nucleos(t)ide analogues (NA) therapy with Hepatitis B surface Antigen (HBsAg) decline less than (<) 0.5 log 10 international unit/milliliter (IU/ml) at baseline received peginterferon alfa-2a 180 microgram (mcg), subcutaneously (SC) once weekly for 48 weeks along with their NA therapy.

Primary: Efficacy: Percent Change From Baseline in Serum Hepatitis B Surface Antigen (HBsAg) Titer at End of the Combination Treatment (Week 48)

End point title	Efficacy: Percent Change From Baseline in Serum Hepatitis B Surface Antigen (HBsAg) Titer at End of the Combination Treatment (Week 48)[1]

End point description:

Intent to Treat (ITT) population included all subjects who received at least one dose of study drug. Here number of subjects analyzed is total number of subjects who were evaluable for this outcome measure.

End point type	Primary

End point timeframe:

Baseline up to 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 performed as planned.

End point values	Pegylated Interferon (Peginterferon) Alfa-2a			
Subject group type	Reporting group			
Number of subjects analysed	69			
Units: percent change				
arithmetic mean (standard deviation)	54.97 (± 31.29)			

Statistical analyses

No statistical analyses for this end point

Primary: Efficacy: Percentage of Subjects With Serum Hepatitis B Surface Antigen (HBsAg) Decrease >/= 50% From Baseline at End of the Combination Treatment (Week 48)

End point title	Efficacy: Percentage of Subjects With Serum Hepatitis B Surface Antigen (HBsAg) Decrease >/= 50% From Baseline at End of the Combination Treatment (Week 48)[2]

End point description:

Subject who stopped pegylated interferon (PEG-IFN) treatment during the add-on phase due to serum HBsAg loss and HBsAg seroconversion were considered as responders. ITT population included all subjects who received at least one dose of study drug. Here number of subjects analyzed is total number of subjects who were evaluable for this outcome measure. The Last Observation Carried

Forward (LOCF) approach was applied to lost-to-follow-up subjects without efficacy measurement at week 48.

End point type	Primary

End point timeframe:

Baseline and Week 48

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: Statistical analysis was not performed as planned.

End point values	Pegylated Interferon (Peginterferon) Alfa-2a			
Subject group type	Reporting group			
Number of subjects analysed	69			
Units: percentage of subjects				
number (not applicable)	43.48			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Adverse Events (AE)

End point title	Number of Subjects With Adverse Events (AE)

End point description:

An AE is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Safety population included all subjects who received least one dose of the study drug and had at least one post-dose safety assessment.

End point type	Secondary

End point timeframe:

Baseline up to Week 48

End point values	Pegylated Interferon (Peginterferon) Alfa-2a			
Subject group type	Reporting group			
Number of subjects analysed	70			
Units: subjects				
number (not applicable)	62			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to Week 48

Adverse event reporting additional description:

Safety population included all subjects who received least one dose of the study drug and had at least one post-dose safety assessment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	Pegylated Interferon (Peginterferon) Alfa-2a

Reporting group description:

Subjects receiving nucleos(t)ide analogues (NA) therapy with Hepatitis B surface Antigen (HBsAg)decline less than <0.5 log 10 international unit/milliliter (IU/ml) at baseline received peginterferon alfa-2a 180 microgram (mcg), subcutaneously (SC) once weekly for 48 weeks along with their NA therapy.

Serious adverse events	Pegylated Interferon (Peginterferon) Alfa-2a		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 70 (7.14%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thyroid cancer			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Rib fracture			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	1 / 70 (1.43%)		
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	Pegylated Interferon (Peginterferon) Alfa-2a		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	56 / 70 (80.00%)		
Nervous system disorders			
Headache			
subjects affected / exposed	17 / 70 (24.29%)		
occurrences (all)	38		
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	7 / 70 (10.00%)		
occurrences (all)	8		
General disorders and administration			

site conditions Asthenia subjects affected / exposed occurrences (all) Irritability subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all) Not coded yet subjects affected / exposed occurrences (all)	 26 / 70 (37.14%) 38 6 / 70 (8.57%) 6 18 / 70 (25.71%) 27 13 / 70 (18.57%) 18		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	 5 / 70 (7.14%) 6		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	 4 / 70 (5.71%) 4		
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	 4 / 70 (5.71%) 4		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	 6 / 70 (8.57%) 7		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Musculoskeletal pain	 6 / 70 (8.57%) 6 6 / 70 (8.57%) 6		

subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all)	10 / 70 (14.29%) 14 14 / 70 (20.00%) 19		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	 4 / 70 (5.71%) 4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 May 2014	1. Amendment was released to recalculate the sample size. 2. This descriptive analysis of the reduction of HBsAg at week 48 was also introduced with the amendment. 3. The amendment also states that subjects with HBsAg loss and seroconversion according to 2012 European Association for the Study of the Liver (EASL) Hepatitis B Virus (HBV) Guidelines during the add-on period would stop both PEG-INF and NA treatments, enter the follow-up period and be considered as responders.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported