



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 | 28 October 2015 |

Results information

| | |
|--------------------------------|--|
| Result version number | v2 (current) |
| This version publication date | 22 October 2016 |
| First version publication date | 10 July 2016 |
| Version creation reason | • Correction of full data set Correction of the data. |

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 | Final |
| Date of interim/final analysis | 28 October 2015 |
| 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 | 28 October 2015 |
| 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 |
| Treated | 70 |
| Completed | 64 |
| Not completed | 12 |
| Started but not Treated | 6 |
| Subject Withdrew Consent | 4 |
| Lost to follow-up | 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 standard deviation | 49.82 ± 8.46 | - | |
| 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:

Per-Protocol Population (PP) included all subjects without severe protocol violations, including major inclusion or exclusion criteria violations.

| | |
|----------------|---------|
| 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: The statistical analysis was not planned to be reported for this endpoint.

| End point values | Pegylated Interferon (Peginterferon) Alfa-2a | | | |
|--------------------------------------|--|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 43 | | | |
| Units: percent change | | | | |
| arithmetic mean (standard deviation) | 59.13 (± 32.14) | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Efficacy: Percentage of Subjects With Serum Hepatitis B Surface Antigen (HBsAg) Decrease \geq 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 \geq 50% From Baseline at End of the Combination Treatment (Week 48) ^[2] |
|-----------------|--|

End point description:

Subjects who stopped pegylated interferon (PEG-IFN) treatment during the add-on phase due to serum HBsAg loss and HBsAg seroconversion were considered as responders. PP included all subjects without severe protocol violations, including major inclusion or exclusion criteria violations and who were undergoing the Week 48 visit.

| | |
|---|---------|
| 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: The statistical analysis was not planned to be reported for this endpoint. | |

| | | | | |
|-------------------------------|--|--|--|--|
| End point values | Pegylated Interferon (Peginterferon) Alfa-2a | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 43 | | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 67.44 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy: Change From Baseline in Serum Hepatitis B Surface Antigen (HBsAg) Titer at Week 24, 72 and 96

| | |
|------------------------------|--|
| End point title | Efficacy: Change From Baseline in Serum Hepatitis B Surface Antigen (HBsAg) Titer at Week 24, 72 and 96 |
| End point description: | Change is calculated by HBsAg titer at baseline - HBsAg titer at week of assessments. PP included all subjects without severe protocol violations, including major inclusion or exclusion criteria violations. Here, number of subjects analyzed signifies those subjects who were evaluable for the outcome measure and n signifies the number of subjects who were evaluated at specified time points. |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 24, 72 and 96 | |

| | | | | |
|---|--|--|--|--|
| End point values | Pegylated Interferon (Peginterferon) Alfa-2a | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 56 | | | |
| Units: international units per millilitre | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n= 56) | 0 (± 0) | | | |
| Change at Week 24 (n= 56) | -546.32 (± 1215.2) | | | |
| Change at Week 72 (n= 55) | -815.69 (± 1394.89) | | | |
| Change at Week 96 (n= 55) | -728.16 (± 1418.6) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy: Percentage of Subjects With HBsAg Decrease ≥ 1 log₁₀ IU/ml From Baseline to Week 48

| | |
|-----------------|--|
| End point title | Efficacy: Percentage of Subjects With HBsAg Decrease ≥ 1 log ₁₀ IU/ml From Baseline to Week 48 |
|-----------------|--|

End point description:

PP included all subjects without severe protocol violations, including major inclusion or exclusion criteria violations and who were undergoing the Week 48 visit.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 48

| End point values | Pegylated Interferon (Peginterferon) Alfa-2a | | | |
|-------------------------------|--|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 43 | | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 13.95 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy: Number of Subjects With Serum HBsAg Loss at Week 12 That Persisted up to Week 96

| | |
|-----------------|--|
| End point title | Efficacy: Number of Subjects With Serum HBsAg Loss at Week 12 That Persisted up to Week 96 |
|-----------------|--|

End point description:

HBsAg loss is defined as HBsAg less than or equal to (\leq) 0.05 IU/ml. PP included all subjects without severe protocol violations, including major inclusion or exclusion criteria violations.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 12 up to Week 96

| | | | | |
|-----------------------------|--|--|--|--|
| End point values | Pegylated Interferon (Peginterferon) Alfa-2a | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 56 | | | |
| Units: subjects | | | | |
| number (not applicable) | 1 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy: HBsAg Levels According to Interleukin 28B (IL28B) Genotypes

| | |
|------------------------|---|
| End point title | Efficacy: HBsAg Levels According to Interleukin 28B (IL28B) Genotypes |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline and Week 48 | |

| | | | | |
|--|--|--|--|--|
| End point values | Pegylated Interferon (Peginterferon) Alfa-2a | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 0 ^[3] | | | |
| Units: international unit/millilitre (IU/mL) | | | | |
| number (not applicable) | | | | |

Notes:

[3] - Analysis was not performed for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy: HBsAg Levels According to Interferon-Inducible Protein 10 (IP-10) Serum Levels

| | |
|------------------------|--|
| End point title | Efficacy: HBsAg Levels According to Interferon-Inducible Protein 10 (IP-10) Serum Levels |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline and Week 48 | |

| End point values | Pegylated Interferon (Peginterferon) Alfa-2a | | | |
|-----------------------------|--|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 0 ^[4] | | | |
| Units: IU/mL | | | | |
| number (not applicable) | | | | |

Notes:

[4] - Analysis was not performed for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Safety: Percentage of Subjects With Adverse Events (AE)

| | |
|--|---|
| End point title | Safety: Percentage 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 | 69 | | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 92.75 | | | |

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 | 17.1 |
|--------------------|------|

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 / 69 (7.25%) | | |
| 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 / 69 (1.45%) | | |
| 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 / 69 (1.45%) | | |
| 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 / 69 (1.45%) | | |
| 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 / 69 (1.45%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endocrine disorders | | | |
| Papillary thyroid cancer | | | |
| subjects affected / exposed | 1 / 69 (1.45%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 1 / 69 (1.45%) | | |
| 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 / 69 (81.16%) | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 19 / 69 (27.54%) | | |
| occurrences (all) | 41 | | |
| Blood and lymphatic system disorders | | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 8 / 69 (11.59%) | | |
| occurrences (all) | 9 | | |
| General disorders and administration site conditions | | | |

| | | | |
|---|--|--|--|
| <p>Asthenia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>27 / 69 (39.13%)</p> <p>39</p> | | |
| <p>Pyrexia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>18 / 69 (26.09%)</p> <p>25</p> | | |
| <p>Fatigue</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>4 / 69 (5.80%)</p> <p>4</p> | | |
| <p>Gastrointestinal disorders</p> <p>Diarrhoea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>5 / 69 (7.25%)</p> <p>6</p> | | |
| <p>Respiratory, thoracic and mediastinal disorders</p> <p>Cough</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>5 / 69 (7.25%)</p> <p>5</p> | | |
| <p>Skin and subcutaneous tissue disorders</p> <p>Pruritus</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>4 / 69 (5.80%)</p> <p>4</p> | | |
| <p>Psychiatric disorders</p> <p>Irritability</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Insomnia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>6 / 69 (8.70%)</p> <p>6</p> <p>7 / 69 (10.14%)</p> <p>8</p> | | |
| <p>Musculoskeletal and connective tissue disorders</p> <p>Arthralgia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Back pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Musculoskeletal pain</p> | <p>6 / 69 (8.70%)</p> <p>6</p> <p>6 / 69 (8.70%)</p> <p>7</p> | | |

| | | | |
|------------------------------------|------------------|--|--|
| subjects affected / exposed | 11 / 69 (15.94%) | | |
| occurrences (all) | 15 | | |
| Myalgia | | | |
| subjects affected / exposed | 15 / 69 (21.74%) | | |
| occurrences (all) | 20 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 6 / 69 (8.70%) | | |
| occurrences (all) | 6 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------|---|
| 29 May 2014 | <ol style="list-style-type: none">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