



Clinical trial results:

Active-controlled phase IIIb study to investigate the ability of the HAP score to predict responders to Octagam 5% in patients with early relapsing multiple sclerosis (PREDICT trial)

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2012-005086-12 |
| Trial protocol | AT HU DE BG PL |
| Global end of trial date | 15 February 2016 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 03 March 2017 |
| First version publication date | 03 March 2017 |

Trial information

Trial identification

| | |
|-----------------------|--------|
| Sponsor protocol code | GAM-27 |
|-----------------------|--------|

Additional study identifiers

| | |
|------------------------------------|----------------|
| ISRCTN number | ISRCTN82177408 |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Octapharma AG |
| Sponsor organisation address | Seidenstraße 2, Lachen, Switzerland, CH-8853 |
| Public contact | Clinical Research Department, Octapharma Pharmazeutika Produktionsgesellschaft m.b. H., +43 161032 1202, barbara.pyringer@octapharma.com |
| Scientific contact | Clinical Research Department, Octapharma Pharmazeutika Produktionsgesellschaft m.b. H., +43 161032 1202, barbara.pyringer@octapharma.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 | 08 February 2017 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 15 February 2016 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to investigate the ability of the HAP score to accurately predict responders to Octagam 5%.

Protection of trial subjects:

This trial was conducted in accordance to the principles of GCP, ensuring that the rights, safety and well-being of patients are protected and in consistency with the Declaration of Helsinki. Inclusion and exclusion criteria were carefully defined in order to protect subjects from contraindications, interactions with other medication and safety factors associated with the investigational medicinal product. Throughout the study safety was assessed, such as occurrence of AEs, lab values, vital signs and physical examinations.

Background therapy:

n.a.

Evidence for comparator:

The active comparator was interferon-beta subcutaneous (IFN- β sc) Betaferon (250 μ g/mL) or glatiramer acetate (GA) Copaxone (20 mg/mL)

The active comparator injections took place at home and were recorded on a patient diary which patients took with them to the study site visits so that the data could be transferred into the eCRF. The visit scheme stayed the same as for IMP-treated patients.

| | |
|---|------------------|
| Actual start date of recruitment | 17 December 2013 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Russian Federation: 87 |
| Country: Number of subjects enrolled | Ukraine: 46 |
| Country: Number of subjects enrolled | Serbia: 1 |
| Country: Number of subjects enrolled | Poland: 2 |
| Country: Number of subjects enrolled | Austria: 1 |
| Country: Number of subjects enrolled | Bulgaria: 33 |
| Country: Number of subjects enrolled | Germany: 3 |
| Country: Number of subjects enrolled | Hungary: 1 |
| Worldwide total number of subjects | 174 |
| EEA total number of subjects | 40 |

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) | 174 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Within 3 weeks, after completion of screening assessments, a blood sample for HAP scoring was analysed and the patient was classified to be a predicted responder or non-responder to Octagam 5% .

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Blinding implementation details:

There was no blinding of the study medication in this study.

In this rater-blinded study, blinding procedures were applicable only to raters.

Arms

| | |
|-----------|---------------|
| Arm title | Overall trial |
|-----------|---------------|

Arm description:

Octagam 5% was to be given every 4 (± 1) weeks at the study site during the 24-month treatment period (i.e., 26 infusions), while active comparator (IFN- β sc/GA) was to be given according to the manufacturer's prescribing information, either at study site or at home every other day (IFN- β 1b sc) or daily (GA).

| | |
|--|-------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Copaxone |
| Investigational medicinal product code | |
| Other name | GA (Glatiramer acetate) |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

GA was to be given according to the manufacturer's prescribing information as a sc daily injection.

| | |
|--|------------------|
| Investigational medicinal product name | Betaferon |
| Investigational medicinal product code | |
| Other name | IFN- β 1b |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

IFN- β 1b was to be given according to the manufacturer's prescribing information as a sc injection every other day.

| | |
|--|--------------------------------|
| Investigational medicinal product name | Octagam 5% |
| Investigational medicinal product code | |
| Other name | Human normal Immunoglobulin 5% |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Octagam 5%, 0.6 g/kg, intravenously (iv) at 4-weekly (± 1 week) intervals.

| Number of subjects in period 1 | Overall trial |
|---------------------------------------|---------------|
| Started | 174 |
| Completed | 0 |
| Not completed | 174 |
| premature termination of study | 174 |

Baseline characteristics

Reporting groups

| | |
|--------------------------------|---------------|
| Reporting group title | Overall trial |
| Reporting group description: - | |

| Reporting group values | Overall trial | Total | |
|---|---------------|-------|--|
| Number of subjects | 174 | 174 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 174 | 174 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 108 | 108 | |
| Male | 66 | 66 | |

End points

End points reporting groups

| | |
|---|-------------------------------------|
| Reporting group title | Overall trial |
| Reporting group description: Octagam 5% was to be given every 4 (± 1) weeks at the study site during the 24-month treatment period (i.e., 26 infusions), while active comparator (IFN- β sc/GA) was to be given according to the manufacturer's prescribing information, either at study site or at home every other day (IFN- β 1b sc) or daily (GA). | |
| Subject analysis set title | Safety population (SAF) - Copaxone |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: subjects treated with Copaxone | |
| Subject analysis set title | Safety population (SAF) - Betaferon |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: subject treated with Betaferon | |
| Subject analysis set title | Safety population (SAF)- Octagam 5% |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: subject treated with Octagam 5% | |
| Subject analysis set title | IFN-b sc/GA |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Comparator group receiving either Betaferon or Copaxone | |

Primary: Heidelberg Assay Panel (HAP) Response Prediction

| | |
|---|---|
| End point title | Heidelberg Assay Panel (HAP) Response Prediction ^[1] |
| End point description: The primary objective of the study was to investigate the ability of the HAP score to accurately predict responders to Octagam 5%. Predicted Responder (HAP score ranging from 0 to 4 points) or predicted non-responder (HAP score ranging from 5 to 9 points). Primary endpoint was superiority with regard to decreased annualised relapse rate (ARR) of Octagam 5% treatment in patients pre-classified as predicted responders compared to predicted non-responders to Octagam 5% treatment. | |
| End point type | Primary |
| End point timeframe: throughout 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: Data didn't support initial assumptions with respect to ARR and therefore all previous considerations of statistical power and sample size are obsolete. Relapses observed are basically distributed uniformly across range of HAP scores with no discernible tendency that patients with a lower HAP score had an increased treatment benefit. This contradicts the initial study assumptions, and is also reflected in an ARR ratio between predicted response and non-response groups close to 1.

| End point values | Safety population (SAF)- Octagam 5% | IFN-b sc/GA | | |
|-----------------------------|-------------------------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 88 | 86 | | |
| Units: Number of patients | | | | |

| | | | | |
|--------------------------|----|----|--|--|
| Predicted Responders | 59 | 60 | | |
| Predicted Non-Responders | 29 | 26 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The condition of the subject was monitored throughout the study. 24 hours SAE reporting requirement.

Adverse event reporting additional description:

All SAEs, suspected to be related to study treatment or not, were reported by telephone, fax or e-mail immediately to the sponsor.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 16.0 |

Reporting groups

| | |
|-----------------------|--------------------------------------|
| Reporting group title | Safety analysis population (Octagam) |
|-----------------------|--------------------------------------|

Reporting group description: -

| | |
|-----------------------|---------------------------------------|
| Reporting group title | Safety analysis population (Copaxone) |
|-----------------------|---------------------------------------|

Reporting group description: -

| | |
|-----------------------|--|
| Reporting group title | Safety analysis population (Betaferon) |
|-----------------------|--|

Reporting group description: -

| Serious adverse events | Safety analysis population (Octagam) | Safety analysis population (Copaxone) | Safety analysis population (Betaferon) |
|---|--------------------------------------|---------------------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 88 (3.41%) | 3 / 54 (5.56%) | 1 / 32 (3.13%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Breast cancer metastatic | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | 0 / 54 (0.00%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pregnancy, puerperium and perinatal conditions | | | |
| Ectopic pregnancy | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | 0 / 54 (0.00%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 54 (1.85%) | 1 / 32 (3.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Renal colic | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | 0 / 54 (0.00%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Chronic tonsillitis | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 54 (1.85%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peritonsillar abscess | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 54 (1.85%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | Safety analysis population (Octagam) | Safety analysis population (Copaxone) | Safety analysis population (Betaferon) |
|---|--------------------------------------|---------------------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 39 / 88 (44.32%) | 25 / 54 (46.30%) | 20 / 32 (62.50%) |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 54 (1.85%) | 2 / 32 (6.25%) |
| occurrences (all) | 0 | 1 | 3 |
| Blood pressure increased | | | |
| subjects affected / exposed | 6 / 88 (6.82%) | 1 / 54 (1.85%) | 0 / 32 (0.00%) |
| occurrences (all) | 8 | 1 | 0 |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 5 / 88 (5.68%) | 0 / 54 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all) | 5 | 0 | 0 |
| Cardiac disorders | | | |

| | | | |
|---|----------------------|------------------------|------------------------|
| Tachycardia subjects affected / exposed occurrences (all) | 5 / 88 (5.68%) 15 | 1 / 54 (1.85%) 1 | 0 / 32 (0.00%) 0 |
| Nervous system disorders | | | |
| Headache subjects affected / exposed occurrences (all) | 4 / 88 (4.55%) 7 | 4 / 54 (7.41%) 19 | 7 / 32 (21.88%) 10 |
| Paraesthesia subjects affected / exposed occurrences (all) | 3 / 88 (3.41%) 3 | 0 / 54 (0.00%) 0 | 2 / 32 (6.25%) 2 |
| Somnolence subjects affected / exposed occurrences (all) | 5 / 88 (5.68%) 12 | 1 / 54 (1.85%) 1 | 0 / 32 (0.00%) 0 |
| General disorders and administration site conditions | | | |
| Asthenia subjects affected / exposed occurrences (all) | 1 / 88 (1.14%) 1 | 3 / 54 (5.56%) 3 | 3 / 32 (9.38%) 4 |
| Influenza like illness subjects affected / exposed occurrences (all) | 1 / 88 (1.14%) 1 | 0 / 54 (0.00%) 0 | 10 / 32 (31.25%) 21 |
| Injection site erythema subjects affected / exposed occurrences (all) | 0 / 88 (0.00%) 0 | 10 / 54 (18.52%) 11 | 5 / 32 (15.63%) 7 |
| Injection site haematoma subjects affected / exposed occurrences (all) | 0 / 88 (0.00%) 0 | 0 / 54 (0.00%) 0 | 2 / 32 (6.25%) 2 |
| Injection site induration subjects affected / exposed occurrences (all) | 0 / 88 (0.00%) 0 | 3 / 54 (5.56%) 5 | 1 / 32 (3.13%) 1 |
| Injection site mass subjects affected / exposed occurrences (all) | 0 / 88 (0.00%) 0 | 3 / 54 (5.56%) 3 | 0 / 32 (0.00%) 0 |
| Injection site pain subjects affected / exposed occurrences (all) | 0 / 88 (0.00%) 0 | 16 / 54 (29.63%) 24 | 3 / 32 (9.38%) 4 |
| Injection site pruritus | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 88 (0.00%) 0 | 3 / 54 (5.56%) 3 | 0 / 32 (0.00%) 0 |
| Pyrexia subjects affected / exposed occurrences (all) | 1 / 88 (1.14%) 3 | 1 / 54 (1.85%) 2 | 3 / 32 (9.38%) 7 |
| Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) | 2 / 88 (2.27%) 2 | 1 / 54 (1.85%) 1 | 3 / 32 (9.38%) 4 |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) | 2 / 88 (2.27%) 4 | 2 / 54 (3.70%) 3 | 2 / 32 (6.25%) 6 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 22 October 2013 | <p>Amendment 1: Amendment #1, dated 22-Oct-2013, described changes made to the original protocol Version 2.0 and was used to create a separate protocol for use in Bulgaria only (Version 3.0). The following changes were made in Amendment #1, to comply with recommendations made by the Bulgarian Drug Agency:</p> <ul style="list-style-type: none">• The in- and exclusion criteria were amended to exclude patients who were at risk of developing side effects of the study medicinal products (active comparators), or of gadolinium, or in whom the active control products were contraindicated.• Continuous mental monitoring with the help of the PHQ-9 questionnaire, a standard and validated tool for assessing and monitoring depression severity, was to be conducted for Bulgarian patients who were to receive active comparator.• The investigator was to discuss further treatment options with the patient already after a first confirmed relapse or a worsening of EDSS by at least 1.0 point confirmed at two assessments separated by at least 12 weeks during the treatment period. After a second confirmed relapse, the patient was to be withdrawn and was to be treated with available medication best suitable for the patient at the Investigator's discretion. |
| 27 November 2013 | <p>Amendment 2: Amendment #2, dated 27-Nov-2013, described changes made to the original protocol Version 2.0 and was used to create a separate protocol for use in Russia only (Version 4.0), to comply with recommendations made by the Russian Drug Agency:</p> <ul style="list-style-type: none">• As the study investigated a theory of validity of use of a HAP score and the drug efficacy within the treatment of MS, it was recommended to change the phase of the study to Phase 2.• The primary endpoint was amended to clearly reflect that the decision on predicted response or predicted non-response was made on the basis of the HAP score. |

| | |
|-----------------|---|
| 22 May 2014 | <p>Amendment 3: Amendment #3, dated 22-May-2014, described changes made to protocol Version 2.0 and was used to create Version 5.0 of the protocol used in all countries except Bulgaria and Russia. This version was used as the basis for this clinical study report. The same changes were incorporated into Version 3.0 of the protocol to produce Version 6.0 for Bulgaria, and into Version 4.0 of the protocol to produce Version 7.0 for Russia.</p> <p>The amendment was issued primarily to incorporate advice from the Steering Committee on the exclusion criteria and support enrolment of patients without biasing the study results with the slightly enlarged study population and to maintain the safety of the participants:</p> <ul style="list-style-type: none"> • The exclusion criterion #2 on excluding patients who had ever had any previous treatment with immunosuppressive agents was amended to a wording that excluded immunosuppressive medication such as azathioprine, mitoxantrone, cyclophosphamide, as well as teriflunomide or fingolimod, in the previous 6 months prior to inclusion in the study. A new exclusion criterion was added to exclude treatment with biological immunosuppressants such as rituximab or similar immune cell depleting therapies in the previous 18 months. • A new exclusion criterion was added: patients with a history of deep vein thrombosis or thrombotic complications after IVIG therapy were excluded to cover for potential predisposition to IVIG side effects. • Clinical response definition had been slightly inconsistent with regard to MRI activity, and was therefore unambiguously stated in a new separate section of the protocol (Section 3.2.4, Clinical Response Definition). • Shipment of blood samples to Heidelberg, Germany for HAP assay was specified to be done on the same day as the blood draw, with arrival at 10 am the following day the latest. • It was clarified that, for the first 50 patients, IMP treatment was to be started only when the Central Laboratory had confirmed arrival of the post-screenin |
| 06 October 2015 | <p>Amendment 4: Amendment #4, dated 06-Oct-2015, described changes made to protocol Version 5.0 and was used to create Version 8.0 of the protocol, used in all countries except Bulgaria and Russia. The same changes were incorporated into Version 6.0 of the protocol to produce Version 9.0 for Bulgaria, and into Version 7.0 of the protocol to produce Version 10.0 for Russia. As the study was prematurely discontinued, no patients were enrolled under this amendment.</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|------------------|---|--------------|
| 09 December 2015 | Early termination of the study due to lack of confirmation of the study assumptions | - |

Notes:

Limitations and caveats

None reported