



## 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- $\beta$  sc) Betaferon (250 $\mu$ 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:

<b>Subjects enrolled per age group</b>	
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 ( $\pm 1$ ) weeks at the study site during the 24-month treatment period (i.e., 26 infusions), while active comparator (IFN- $\beta$  sc/GA) was to be given according to the manufacturer's prescribing information, either at study site or at home every other day (IFN- $\beta$  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- $\beta$ 1b
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

IFN- $\beta$  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 ( $\pm 1$  week) intervals.

<b>Number of subjects in period 1</b>	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 ( $\pm 1$ ) weeks at the study site during the 24-month treatment period (i.e., 26 infusions), while active comparator (IFN- $\beta$ sc/GA) was to be given according to the manufacturer's prescribing information, either at study site or at home every other day (IFN- $\beta$ 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 <sup>[1]</sup>
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: -

<b>Serious adverse events</b>	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 %

<b>Non-serious adverse events</b>	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"><li>• 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.</li><li>• 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.</li><li>• 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.</li></ul>
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"><li>• 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.</li><li>• 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.</li></ul>

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"> <li>• 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.</li> <li>• 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.</li> <li>• 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).</li> <li>• 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.</li> <li>• 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</li> </ul>
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