



## Clinical trial results: Immune tolerance induction in MS patients with neutralizing antibodies against interferon-beta

### Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2009-013284-19    |
| Trial protocol           | AT                |
| Global end of trial date | 30 September 2010 |

### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 21 October 2020 |
| First version publication date | 21 October 2020 |

### Trial information

#### Trial identification

|                       |            |
|-----------------------|------------|
| Sponsor protocol code | HINABS-ITI |
|-----------------------|------------|

#### Additional study identifiers

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

Notes:

### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Medical University Innsbruck   |
| Sponsor organisation address | Christoph-Probst-Platz 1, Innrain 52 A, Innsbruck, Austria, 6020   |
| Public contact               | Priv.Do. Dr. Harald Hegen, Medical University Innsbruck, University Hospital for Neurology, +43 (0)512- 504- 24279, harald.hegen@tirol-kliniken.at |
| Scientific contact           | Priv.Do. Dr. Harald Hegen, Medical University Innsbruck, University Hospital for Neurology, +43 (0)512- 504- 24279, harald.hegen@tirol-kliniken.at |

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                       | 30 September 2010 |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 30 September 2010 |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 30 September 2010 |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

How many multiple sclerosis patients show a reduction of the neutralizing antibodies < 100 neutralizing units after 3 months of weekly intravenous interferon-beta infusion.

Protection of trial subjects:

To reduce side effects such as flu-like symptoms (FLS), 1000 mg paracetamol were administered intravenously prior to each IFN $\beta$  infusion.

Background therapy:

All subjects received IFN $\beta$  before enrolled in the trial.

Evidence for comparator:

No comparators were tested in this trial.

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 10 December 2009 |
| 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 | Austria: 10 |
| Worldwide total number of subjects   | 10          |
| EEA total number of subjects         | 10          |

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)                      | 10 |
| From 65 to 84 years                       | 0  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Patients were eligible if they were diagnosed as relapsing MS or clinically isolated syndrome (CIS) according to the revised McDonalds criteria 2005, received previous treatment with any IFN $\beta$  preparation and were NAb positive with a titer >500 TRU (10-fold reduction unit) at screening.

### Pre-assignment

Screening details:

Previous IFN $\beta$  treatment had to be interrupted for at least 7 days before baseline visit. Patients, who did not show sufficient MxA gene expression after administration of the study dose of 1500 $\mu$ g IFN $\beta$ -1b at baseline or at week 1, were withdrawn from the study.

### Period 1

|                              |                  |
|------------------------------|------------------|
| Period 1 title               | Treatment period |
| Is this the baseline period? | Yes              |
| Allocation method            | Not applicable   |
| Blinding used                | Not blinded      |

### Arms

|                  |                           |
|------------------|---------------------------|
| <b>Arm title</b> | IFN $\beta$ -1b treatment |
|------------------|---------------------------|

Arm description:

We aimed to investigate whether the repeated high-dose intravenous IFN $\beta$  administration in patients with high NAb titers leads to a sustained reversion of NABs and an increase of MxA expression

|  |                                  |
|--|----------------------------------|
| Arm type                               | Experimental                     |
| Investigational medicinal product name | Interferon Beta-1b               |
| Investigational medicinal product code |                                  |
| Other name                             | Betaferon                        |
| Pharmaceutical forms                   | Powder for solution for infusion |
| Routes of administration               | Intravenous use                  |

Dosage and administration details:

Subjects received 1500 $\mu$ g IFN $\beta$ -1b reconstituted in 100 ml 0.9% NaCl intravenously once a week over 3 months (i.e. a total of 13 infusions).

| Number of subjects in period 1 | IFN $\beta$ -1b treatment |
|--------------------------------|---------------------------|
| Started                        | 10                        |
| Completed                      | 9                         |
| Not completed                  | 1                         |
| Lacking MxA induction          | 1                         |

**Period 2**

|                              |                  |
|------------------------------|------------------|
| Period 2 title               | Follow-up period |
| Is this the baseline period? | No               |
| Allocation method            | Not applicable   |
| Blinding used                | Not blinded      |

**Arms**

|                  |                           |
|------------------|---------------------------|
| <b>Arm title</b> | IFN $\beta$ -1b follow-up |
|------------------|---------------------------|

## Arm description:

We aimed to investigate whether the repeated high-dose intravenous IFN $\beta$  administration in patients with high NAb titers leads to a sustained reversion of NABs and an increase of MxA expression

|  |                                  |
|--|----------------------------------|
| Arm type                               | Experimental                     |
| Investigational medicinal product name | Interferon Beta-1b               |
| Investigational medicinal product code |                                  |
| Other name                             | Betaferon                        |
| Pharmaceutical forms                   | Powder for solution for infusion |
| Routes of administration               | Intravenous use                  |

## Dosage and administration details:

Subjects received 1500 $\mu$ g IFN $\beta$ -1b reconstituted in 100 ml 0.9% NaCl intravenously once a week over 3 months (i.e. a total of 13 infusions).

|                                       |                           |
|---------------------------------------|---------------------------|
| <b>Number of subjects in period 2</b> | IFN $\beta$ -1b follow-up |
| Started                               | 9                         |
| Completed                             | 9                         |

## Baseline characteristics

### Reporting groups

|                       |                           |
|-----------------------|---------------------------|
| Reporting group title | IFN $\beta$ -1b treatment |
|-----------------------|---------------------------|

Reporting group description:

We aimed to investigate whether the repeated high-dose intravenous IFN $\beta$  administration in patients with high NAb titers leads to a sustained reversion of NAbS and an increase of MxA expression

| Reporting group values                             | IFN $\beta$ -1b treatment | Total |  |
|--|---------------------------|-------|--|
| Number of subjects                                 | 10                        | 10    |  |
| 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)                               | 10                        | 10    |  |
| From 65-84 years                                   | 0                         | 0     |  |
| 85 years and over                                  | 0                         | 0     |  |
| Age continuous                                     |                           |       |  |
| Units: years                                       |                           |       |  |
| arithmetic mean                                    | 47.4                      |       |  |
| standard deviation                                 | $\pm 10.019$              | -     |  |
| Gender categorical                                 |                           |       |  |
| Units: Subjects                                    |                           |       |  |
| Female   | 5                         | 5     |  |
| Male   | 5                         | 5     |  |

## End points

### End points reporting groups

|  |                           |
|--|---------------------------|
| Reporting group title  | IFN $\beta$ -1b treatment |
| Reporting group description:<br>We aimed to investigate whether the repeated high-dose intravenous IFN $\beta$ administration in patients with high NAb titers leads to a sustained reversion of NAb and an increase of MxA expression |                           |
| Reporting group title  | IFN $\beta$ -1b follow-up |
| Reporting group description:<br>We aimed to investigate whether the repeated high-dose intravenous IFN $\beta$ administration in patients with high NAb titers leads to a sustained reversion of NAb and an increase of MxA expression |                           |

### Primary: NAb titer

|   |           |
|---|-----------|
| End point title   | NAb titer |
| End point description:<br>Blood collections were performed at screening, then monthly at baseline, week 4, 8 and 12, as well as at follow-up after 24 weeks. At baseline and weeks 4, 8 and 12 blood samples were withdrawn immediately before and 4h after IFN $\beta$ administration. |           |
| End point type  | Primary   |
| End point timeframe:<br>Day 0 (baseline)- week 24   |           |

| End point values                      | IFN $\beta$ -1b treatment | IFN $\beta$ -1b follow-up |  |  |
|---------------------------------------|---------------------------|---------------------------|--|--|
| Subject group type                    | Reporting group           | Reporting group           |  |  |
| Number of subjects analysed           | 9                         | 9                         |  |  |
| Units: TRU                            |                           |                           |  |  |
| median (inter-quartile range (Q1-Q3)) | 1429 (902 to 2995)        | 2175 (1803 to 2519)       |  |  |

### Statistical analyses

|  |   |
|--|---|
| Statistical analysis title   | NAb titers  |
| Statistical analysis description:<br>Median NAb titer at follow-up was not significantly different compared to baseline. |   |
| Comparison groups  | IFN $\beta$ -1b treatment v IFN $\beta$ -1b follow-up |
| Number of subjects included in analysis  | 18  |
| Analysis specification   | Pre-specified   |
| Analysis type  | superiority   |
| P-value  | = 0.23  |
| Method   | Wilcoxon (Mann-Whitney)                               |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Week 0- week 24

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

### Dictionary used

|                 |       |
|-----------------|-------|
| Dictionary name | CTCAE |
|-----------------|-------|

|                    |      |
|--------------------|------|
| Dictionary version | 4.03 |
|--------------------|------|

### Reporting groups

|                       |   |
|-----------------------|---|
| Reporting group title | IFN $\beta$ -1b treatment and follow-up |
|-----------------------|---|

Reporting group description:

We aimed to investigate whether the repeated high-dose intravenous IFN $\beta$  administration in patients with high NAb titers leads to a sustained reversion of NAb and an increase of MxA expression

| Serious adverse events                            | IFN $\beta$ -1b treatment and follow-up |  |  |
|---|---|--|--|
| Total subjects affected by serious adverse events |   |  |  |
| subjects affected / exposed                       | 0 / 10 (0.00%)                          |  |  |
| number of deaths (all causes)                     | 0                                       |  |  |
| number of deaths resulting from adverse events    | 0                                       |  |  |

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

| Non-serious adverse events                            | IFN $\beta$ -1b treatment and follow-up |  |  |
|---|---|--|--|
| Total subjects affected by non-serious adverse events |   |  |  |
| subjects affected / exposed                           | 5 / 10 (50.00%)                         |  |  |
| Cardiac disorders                                     |   |  |  |
| Hypotonia   |   |  |  |
| subjects affected / exposed                           | 1 / 10 (10.00%)                         |  |  |
| occurrences (all)                                     | 1                                       |  |  |
| Immune system disorders                               |   |  |  |
| Relapse   |   |  |  |
| subjects affected / exposed                           | 1 / 10 (10.00%)                         |  |  |
| occurrences (all)                                     | 1                                       |  |  |
| Respiratory, thoracic and mediastinal disorders       |   |  |  |
| Flu-like symptoms                                     |   |  |  |

|  |                      |  |  |
|--|----------------------|--|--|
| subjects affected / exposed<br>occurrences (all)   | 1 / 10 (10.00%)<br>1 |  |  |
| Infections and infestations<br>Respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 2 / 10 (20.00%)<br>2 |  |  |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/25878009>