Clinical Study Synopsis

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### Clinical Trial Results Synopsis

**Study Design Description**

<table>
<thead>
<tr>
<th>Study Sponsor:</th>
<th>Bayer HealthCare AG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Number:</td>
<td>91489 (308084) NCT00317941 EudraCT 2005-005583-91</td>
</tr>
<tr>
<td>Study Phase:</td>
<td>IV Interventional</td>
</tr>
<tr>
<td>Official Study Title:</td>
<td>The AVANTAGE study - A randomized, multicenter, phase IV, open-label prospective study comparing injection site reaction and injection site pain in patients with relapsing remitting multiple sclerosis (RRMS) or after a first demyelinating event suggestive of MS newly started on interferon beta-1b (Betaferon®) or interferon beta-1a (Rebif®).</td>
</tr>
<tr>
<td>Therapeutic Area:</td>
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**Test Product**

<table>
<thead>
<tr>
<th>Name of Test Product:</th>
<th>Interferon beta-1b (Betaferon, BAY86-5046) Interferon beta-1a (Rebif)</th>
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</thead>
<tbody>
<tr>
<td>Name of Active Ingredient:</td>
<td>Interferon beta-1b Interferon beta-1a</td>
</tr>
<tr>
<td>Dose and Mode of Administration:</td>
<td>Interferon beta-1b (IFNB-1b): A dose of 250 µg (8 MIU) every other day was injected subcutaneously using Betaject® or Betaject® Light. Interferon beta-1a (IFNB-1a): A dose of 44 µg (12 MIU) three times a week was injected subcutaneously using Rebiject II™.</td>
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</tbody>
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**Reference Therapy/Placebo**

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Dose and Mode of Administration:</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

**Duration of Treatment:**

- Treatment was given for up to 3 months.

**Studied period:**

- Date of first subject’s first visit: 09 MAR 2006
- Date of last subject’s last visit: 09 APR 2008

**Premature Study Suspension / Termination:**

- No

**Substantial Study Protocol Amendments:**

- The study was conducted according to the final approved study protocol (dated 05 DEC 2005) and its four amendments:

  Amendment No. 1 (dated 09 OCT 2006) specified the following change:
Study was updated with the new approved indication for interferon beta-1b (subjects with high risk of developing multiple sclerosis [MS]).

Amendment No. 2 (dated 19 MAR 2007) specified the following change:

Inclusion period was extended to 31 DEC 2007 due to the low rate of recruitment.

Amendment No. 4 (dated 05 SEP 2007) specified the following change:

Because of new presentations of the study drugs and investigators’ requests, it was important to verify the robustness of the conclusions of the study by means of a supplementary examination of the reactions and pain observed at the injection site using the new systems. The supplementary examination consisted of a comparison between two pilot groups of subjects using the products in their new presentation.

| Study Centre(s): | The study was conducted at 61 investigational sites in France. |
| Methodology: | In this study, subjects were randomly assigned to three treatment arms: |
| | • Arm 1: Interferon beta-1b 250 µg via Betaject® |
| | • Arm 2: Interferon beta-1b 250 µg via Betaject® Light |
| | • Arm 3: Interferon beta-1a 44 µg via Rebiject II™ |

The study lasted at least 3 months with 4 visits: V0 (inclusion), V1 (end of Month 1), V2 (end of Month 2), V3 (end of Month 3). Subjects underwent physical examination, assessment for relapse of MS, evaluation of injection site reactions (ISRs), and injection site pain (ISP) by the physicians and by the subjects (on the basis of logbooks), and evaluation of compatibility of treatment, adverse events (AEs), and concomitant treatment at each of the three end of month visits (V1, V2, and V3).

Subjects received a diary for each month of administration. They made a self-assessment of ISR 24 hours and 48 hours after the injection by noting whether there was any redness, and by choosing an appropriate option that explained the intensity of the inflammatory reaction [0 = lack of redness or limited redness at the injection site (no redness), 1 = skin is moderately pink (erythema), 2 = skin is red (edema), 3 = swelling with redness (infiltration/induration), 4 = lesion at the injection site: impaired skin and tissue destruction (necrosis/ulceration)]. Subjects also self-assessed pain immediately after injection, and 30 min, 1 h, and 24 h after administration of treatment using the visual analog scale (VAS). The parameters of safety (AEs/serious adverse events [SAEs]) were recorded at each visit.

| Indication/Main Inclusion Criteria: | Indication: Relapsing-remitting multiple sclerosis |
| | Inclusion criteria: |
| | • Both female and male subjects |
| | • Subjects ≥ 18 years of age |
- Subjects with first clinical demyelinating event suggestive of MS or confirmed diagnosis of RRMS
- Subjects prescribed subcutaneously administered beta-interferon for the first time
- For female subjects of child-bearing potential, subjects who agreed to practice adequate contraception methods over the entire study period
- Subjects capable of following the study all along and respecting all recommended procedures mentioned in the study protocol
- Subjects for whom laboratory evaluations were available with normal liver function test and normal complete blood count with differential count
- Subjects who have given written informed consent

**Study Objectives:**

**Primary:**
To compare occurrence, intensity, and frequency of ISRs in subjects with RRMS or after a first clinical demyelinating event suggestive of MS newly started on IFNB-1b versus IFNB-1a.

**Secondary:**
- To evaluate injection tolerability during IFNB-1b or IFNB-1a treatment (comparison between the products)
- To compare the auto-injectors used (Betaject®, Betaject® Light, and Rebiject II™) (comparison between the auto-injectors)

**Evaluation Criteria:**

**Efficacy (Primary):**
- Percentage of the sites developing an ISR reported by subjects 24 hours after each injection (assessed up to 3 months). An injection site was considered as developing a reaction if the subject's score for this site was of a reaction intensity ≥ 1. The numbers of injection sites per month per subject were analyzed.
- Percentage of the sites developing an ISR reported by subjects 48 hours after each injection (assessed up to 3 months). An injection site was considered as developing a reaction if the subject's score for this site was of a reaction intensity ≥ 1. The numbers of injection sites per month per subject were analyzed.
- Mean scores of reaction after injection reported by subjects (assessed every 24 hours and 48 hours after each injection for up to 3 months). Scores ranged from 0 to 4, where 0 = no abnormal reaction, 1 = erythema, 2 = edema, 3 = infiltration, and 4 = ulceration or necrosis.
- Other prespecified variables: Mean scores of reaction after injection reported by subjects between different auto-injectors (assessed up to 3 months). Scores ranged from 0 to 4, where 0 = no abnormal reaction, 1 = erythema, 2 = edema, 3 = infiltration, and 4 = ulceration or necrosis.

**Efficacy (Secondary):**
- Percentage of injection sites with pain reported by physicians (assessed up to 3 months)
- Percentage of injection site with reaction per subject reported by physicians (assessed up to 3 months)
- Percentage of subjects without ISR reported by subjects
(assessed every 24 hours after each injection up to 3 months)

- Percentage of sites developing a severe reaction 24 hours after injection (assessed up to 3 months). An ISR was considered severe if the score reported by the subject was above 2 (at least 1 red skin)
- Percentage of sites developing a severe reaction 48 hours after injection (assessed up to 3 months). An ISR was considered severe if the score reported by the subject was above 2 (at least 1 red skin)
- Percentage of subjects without pain reported by subjects (assessed every 24 hours after each injection up to 3 months)
- Percentage of injection sites without pain reported by physicians (assessed up to 3 months)
- Percentage of injection sites without pain reported by subjects (assessed every 24 hours after each injection up to 3 months)
- Mean pain assessment using VAS reported by subjects immediately after injection. Visual analog scale was used to report the pain from 0 (no pain) to 10 (maximal pain)
- Mean pain assessment using VAS reported by subjects 30 min after injection. Visual analog scale was used to report the pain from 0 (no pain) to 10 (maximal pain)
- Mean pain assessment using VAS reported by subjects 1 h after injection. Visual analog scale was used to report the pain from 0 (no pain) to 10 (maximal pain)
- Mean pain assessment using VAS reported by subjects 24 h after injection. Visual analog scale was used to report the pain from 0 (no pain) to 10 (maximal pain)
- Percentage of sites without reaction 24 hours after injection reported by subjects (assessed up to 3 months)
- Percentage of sites without reaction 48 hours after injection reported by subjects (assessed up to 3 months)

**Safety:**

Tolerance variable: Adverse events

<table>
<thead>
<tr>
<th><strong>Statistical Methods:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population:</strong></td>
</tr>
<tr>
<td>All randomized analysis set: All subjects randomized to treatment. Full analysis set: All randomized subjects with at least one administration of the study drug. This analysis set constituted the primary analysis set for safety analysis. Per-protocol analysis set: Individual data from subjects with an end of study (EOS) after Month 1. This analysis set constituted the primary analysis set for the endpoints evaluation (i.e., 14 injections for IFNB-1b or 12 injections for IFNB-1a).</td>
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</table>

**Efficacy (Primary):**

Statistical analysis was carried out for the entire 3 month period, and then for each month. Efficacy variables were analyzed in an exploratory or descriptive manner.

Comparative analysis was first carried out for the two products: IFNB-1b versus IFNB-1a, and then for the three auto-injectors: Betaject®, Betaject® Light, and Rebiject II™.
Quantitative variables were described by mean, standard deviation (SD), median, range, 95% confidence interval, number of missing values, and the size of each class. Qualitative variables were presented in terms of size and percentage of each class, and the number of missing values.

For comparative analysis, Student’s t-test, Chi-square test, Wilcoxon signed-rank test, Kruskal-Wallis test, analysis of variance (ANOVA), and general linear model (GLM) were used.

**Efficacy (Secondary):**
Statistical analysis was carried out in the same way as for primary efficacy variables.

**Safety:**
Statistical analysis was carried out for the entire 3 month period and then for each month. Safety variables were analyzed using descriptive statistics.

<table>
<thead>
<tr>
<th>Number of Subjects:</th>
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<tbody>
<tr>
<td>Total number of subjects screened: 220</td>
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<tr>
<td>Total number of subjects randomized: 220</td>
</tr>
<tr>
<td>Total number of subjects in Arm 1: 73</td>
</tr>
<tr>
<td>Total number of subjects in Arm 2: 79</td>
</tr>
<tr>
<td>Total number of subjects in Arm 3: 68</td>
</tr>
</tbody>
</table>

### Study Results

**Results Summary — Subject Disposition and Baseline**

A total of 220 subjects were recruited in 61 centers in France and randomized to receive either IFNB-1b (152 subjects) or IFNB-1a (68 subjects); treatments were started by a total 220 subjects (IFNB-1b: 152; IFNB-1a: 68). A total of 196 subjects (90% of the full randomized set) completed the 3-month trial (91% in the IFNB-1b group and 85% in the IFNB-1a group). The difference was not statistically significant. These low drop-out rates were regarded as a reflection of both the good tolerability of the study treatments and the good quality of the study conduct. In the IFNB-1b group, a lower drop-out rate was observed than in IFNB-1a group (p-value: 0.173). The overall adherence to the treatment was about 93% and 89% in IFNB-1b and IFNB-1a groups, respectively, which was not statistically different (p-value: 0.205).

For analysis, the following analysis sets were used:

<table>
<thead>
<tr>
<th>Analysis Set</th>
<th>IFNB-1b</th>
<th>IFNB-1a</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>All randomized set</td>
<td>152 (100%)</td>
<td>68 (100%)</td>
<td>220 (100%)</td>
</tr>
<tr>
<td>Full analysis set</td>
<td>150 (98.7%)</td>
<td>65 (95.6%)</td>
<td>215 (97.7%)</td>
</tr>
<tr>
<td>Safety analysis</td>
<td>150 (98.7%)</td>
<td>65 (95.6%)</td>
<td>215 (97.7%)</td>
</tr>
<tr>
<td>Per-protocol set</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After 1 month</td>
<td>142 (93.4%)</td>
<td>63 (92.6%)</td>
<td>205 (93.2%)</td>
</tr>
<tr>
<td>EOS / Month 3</td>
<td>138 (90.8%)</td>
<td>58 (85.3%)</td>
<td>196 (89.1%)</td>
</tr>
</tbody>
</table>

There were no relevant group differences in any of the demographic parameters. In the per-protocol set (after 1 month), 75% of the subjects were females (52 males [36 males who received IFNB-1b, 16 males who received IFNB-1a] and 153 females [106 females who received IFNB-1b, 47 females who received IFNB-1a]); their mean age was
superior to IFNB
Results Summary — Efficacy

Primary endpoints: As the primary endpoint, the study results revealed that IFNB-1b was superior to IFNB-1a with respect to ISR reported by subjects.

- Percentage of sites developing an ISR 24 hours after injection reported by subjects: Overall, 16 injection sites per month per subject were analyzed in both the groups. Overall results (for the entire study period) revealed that 30.7 ± 1.73% of sites per subject in the IFNB-1b group and 37.0 ± 1.74% of the sites per subject in the IFNB-1a group developed an ISR 24 hours after an injection. The difference was not statistically significant (p = 0.18).

- Percentage of sites developing an ISR 48 hours after each injection reported by subjects: Overall, 16 injection sites per month per subject were analyzed in both the groups. The difference was statistically significant immediately after the second month. At the end of the third month, 28.3% (IFNB-1b group) versus 45.4% (IFNB-1a group) of the sites developed a reaction (p = 0.0031) 48 h after injection. Overall results (for the entire study period) revealed that 27.3 ± 1.60% of the sites in the IFNB-1b and 40.8 ± 1.85% of the sites in the IFNB-1a developed an ISR 48 hours after injection. The difference was statistically significant (p = 0.0033).

- Mean scores of reaction after injection by subjects: The intensity of ISR reported by subjects was lower in IFNB-1b than in IFNB-1a subjects at the end of the first month (0.338 ± 1.73 IFNB-1b group, 0.412 ± 2.07 IFNB-1a group; p = 0.23), second month (0.391 ± 2.22 IFNB-1b group, 0.540 ± 2.25 IFNB-1a group; p = 0.048), and third month (0.376 ± 2.10 IFNB-1b group, 0.554 ± 2.31 IFNB-1a group; p = 0.02). The difference was statistically significant after the second and third months and for the entire study period (0.368 ± 3.11 IFNB-1b group, 0.500 ± 3.45 IFNB-1a group; p = 0.039).

- Other prespecified variables: Mean score of reaction after injection reported by subjects between different auto-injectors was 0.372 ± 2.82 for Betaject®, 0.363 ± 3.34 for Betaject® Light, and 0.5 ± 3.45 for Rebiject II™.

Secondary endpoints:

- Percentage of injection sites with pain reported by physicians: Overall (for the entire study period), the percentage of sites with pain was 6.2 ± 0.88% in the IFNB-1b group and 5.2 ± 0.70% in the IFNB-1a group. The difference was not statistically significant (p = 0.63).

- Percentage of injection site with reaction per subject reported by physicians: Overall (for the entire study period), the percentage of ISR per subject was 14.1% in the IFNB-1b group and 18.6% in the IFNB-1a group. The difference was not statistically significant.

- Percentage of subjects without ISR reported by subjects: Overall (for the entire study period), the percentage of subjects without ISR was 21.3% in the IFNB-1b group and 9.5% in the IFNB-1a group.

- Percentage of sites developing a severe reaction 24 hours after injection: Overall (for the entire study period), the percentage of sites with a severe reaction 24 hours after injection was 6.1 ± 0.769% in the IFNB-1b group and 8.45 ± 0.896% in the IFNB-1a group. The difference was not statistically significant.
- Percentage of sites developing a severe reaction 48 hours after injection: Overall (for the entire study period), the percentage of sites with a severe reaction 48 hours after injection was 4.97 ± 0.576% in the IFNB-1b group and 8.76 ± 0.905% in the IFNB-1a group. The difference was not statistically significant.

- Percentage of subjects without pain reported by subjects: Overall (for the entire study period), the percentage of subjects without pain reported by subjects was 5.6% in the IFNB-1b group and 17.7% in the IFNB-1a group.

- Percentage of injection sites without pain reported by physicians: Overall (for the entire study period), the percentage of injection sites without pain reported by physicians was 85.9 ± 1.27% in the IFNB-1b group and 81.4 ± 0.15% in the IFNB-1a group. The difference was not statistically significant.

- Percentage of injection sites without pain reported by subjects: Overall (for the entire study period), the percentage of injection sites without pain reported by subjects was 30.3% in the IFNB-1b group and 42.0% in the IFNB-1a group.

- Mean pain assessment using VAS reported by subjects immediately after injection: Overall (for the entire study period), the mean pain score using VAS reported by subjects immediately after injection was 1.2 ± 9.10 in the IFNB-1b group and 1.45 ± 8.80 in the IFNB-1a group. The difference was not statistically significant.

- Mean pain assessment using VAS reported by subjects 30 min after injection: Overall (for the entire study period), the mean pain score using VAS reported by subjects 30 min after injection was 0.705 ± 7.26 in the IFNB-1b group and 0.846 ± 7.29 in the IFNB-1a group. The difference was not statistically significant.

- Mean pain assessment using VAS reported by subjects 1 h after injection: Overall (for the entire study period), the mean pain score using VAS reported by subjects 60 min after injection was 0.574 ± 6.11 in the IFNB-1b group and 0.666 ± 7.52 in the IFNB-1a group. The difference was not statistically significant.

- Mean pain assessment using VAS reported by subjects 24 h after injection: Overall (for the entire study period), the mean pain score using VAS reported by subjects 24 hours after injection was 0.641 ± 6.74 in the IFNB-1b group and 0.581 ± 6.45 in the IFNB-1a group. The difference was not statistically significant.

- Percentage of sites without reaction 24 hours after injection reported by subjects: Overall (for the entire study period), the percentage of sites without reaction 24 hours after injection reported by subjects was 62.2% in the IFNB-1b group and 63.0% in the IFNB-1a group.

- Percentage of sites without reaction 48 hours after injection reported by subjects: Overall (for the entire study period), the percentage of sites without reaction 48 hours after injection reported by subjects was 71.8% in the IFNB-1b group and 54.6% in the IFNB-1a group.

Concerning the secondary endpoints, this study did not show any significant difference between the two groups of treatment for ISR or ISP.

**Results Summary — Safety**

A total of 125 subjects presented at least one AE (58%).

In this population, 93 subjects presented at least one drug-related AE (74%). There were no relevant differences between the treatment groups for the frequency of AEs. However, an absolute difference of 10% in the proportion of IFNB-1a subjects affected compared to IFNB-1b was observed for AEs. Ten subjects had AEs which led to withdrawal/discontinuation of the study (3.3% of the subjects in IFNB-1b group and 7.7% of the subjects in IFNB-1a group). These results can be regarded as a reflection of an overall acceptable tolerability of the study drugs.
No significant difference (p > 0.05) could be observed between both the treatments when considering the relevant AEs reported by the physicians (drug-related or not related). Concerning the MS relapse, asthenia, hematologic troubles, myalgia, fever, sleep disturbance, and pain, IFNB-1b treatment was as acceptable as IFNB-1a, though the difference was not statistically significant. The frequency of drug-related AEs linked to general trouble was lower in the IFNB-1b treatment (51.8% versus 76.2%), though the difference was not statistically significant (p > 0.05).

The frequency of drug-related AEs was also not significantly different between the treatment groups (p = 0.34).

No deaths were reported during the study. Three serious AEs were reported:
- Cytolytic hepatitis (treatment given: IFNB-1b, moderate intensity, study drug relationship: possible, study drug withdrawn)
- Acute coronary syndrome (treatment given: IFNB-1a, severe intensity, not related to the study drug, study drug dose not changed)
- Lumbago (treatment given: IFNB-1b, moderate intensity, not related to the study drug, study drug dose not changed)

**Conclusion(s)**

This study demonstrates that relative to IFNB-1a treatment, IFNB-1b treatment resulted in statistically significantly less ISRs and mean scores of ISRs as reported by subjects based on the primary endpoints. No overall difference existed between the three auto-injectors on the primary endpoint related to mean score of ISR reported by the subjects. Drug-related AEs were not significantly different in both the treatment arms.

<table>
<thead>
<tr>
<th>Publication(s):</th>
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</thead>
<tbody>
<tr>
<td>Date Created or Date Last Updated:</td>
<td>10 MAY 2013</td>
</tr>
</tbody>
</table>