Amsterdam, 27 March 2025
EMADOC-1700519818-1850245
Human Medicines Division

# Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

## Avonex

Interferon beta-1A

Procedure no: EMA/PAM/0000245472

## Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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# 1. Introduction

On 13 January 2025, the MAH submitted an interim report of a paediatric study for Avonex, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. These data are also submitted as part of the post-authorisation measure specific obligation.

The MAH submits an interim report for Study 105MS306 (CHARGE), "An Open-label, randomized, multicenter, active-controlled, parallel-group study to evaluate the safety, tolerability and efficacy of BIIB017 in paediatric subjects aged 10 to less than 18 years for the treatment of relapsing remitting multiple sclerosis (RRMS), with optional open-label extension". This interim clinical study report provides the interim analysis results for part 1 of the study through week 48, referred to as the part 1a analysis. A second interim analysis with data through week 96 of treatment (part 1a+1b) is planned to be submitted and reported in a separate interim report. The open label extension period of the study (up to week 192) will be reported in the final clinical study report upon study completion.

This study is part of the agreed paediatric investigation plan for peginterferon beta-1a (EMEA-001129-PIP01-M06) and the same submission has been done for Plegridy (peginterferon beta-1a; BIIB017). For the present procedure the relevant data are those from Avonex, used as a comparator in the study. Last subject last visit for Part 1a (week 48) for the study occurred on 18 July 2024.

A short critical expert overview has not been provided, neither a discussion on how the data submitted may influence the current benefit-risk balance of Avonex or have further regulatory consequences.

***CHMP comments***

*The MAH submits an interim report for Study 105MS306 including the results for part 1 of the study through week 48 (referred to as the part 1a analysis). It is understood that the study is still ongoing. Only part 1a of the study (treatment period through week 48) is part of the peginterferon beta-1a PIP.*

# 2. Scientific discussion

## *2.1. Information on the development program*

Study 105MS306, "An Open-label, randomized, multicenter, active-controlled, parallel-group study to evaluate the safety, tolerability and efficacy of BIIB017 in paediatric subjects aged 10 to less than 18 years for the treatment of relapsing remitting multiple sclerosis, with optional open-label extension" (Part 1, referred to as the Part 1a analysis) is submitted as a stand-alone study. Study 105MS306 assesses the efficacy and safety of peginterferon beta-1a in children, in accordance with the agreed PIP (EMEA-001129-PIP01-M06).

## *2.2. Information on the pharmaceutical formulation used in the study*

Avonex was supplied as an auto-injector pen for IM administration once weekly in countries in which the Avonex Pen is approved. In countries where the Avonex Pen was not approved, the Avonex Prefilled Syringe was provided. Avonex doses were titrated during the first 4 weeks of the study treatment period using the Avostartgrip titration kit.

***CHMP comments***

*As reflected in the SmPC, although the safety and efficacy of Avonex in children and adolescents aged 10 to 18 years have not yet been fully established, there is experience with the use of the currently marketed formulation of Avonex® (30 micrograms/0.5ml solution for injection; 30 micrograms/0.5ml*

*solution for injection in pre-filled pen) in paediatric patients, with an acceptable safety profile. None of the excipients is known to have safety concerns used as intended in paediatric patients.*

## *2.3. Clinical aspects*

### 2.3.1. Introduction

The MAH submitted an interim report for Study 105MS306 (CHARGE), "An Open-label, randomized, multicenter, active-controlled, parallel-group study to evaluate the safety, tolerability and efficacy of BIIB017 in paediatric subjects aged 10 to less than 18 years for the treatment of relapsing remitting multiple sclerosis, with optional open-label extension"

### 2.3.2. Clinical study

### Study 105MS306

"An Open-label, randomized, multicenter, active-controlled, parallel-group study to evaluate the safety, tolerability and efficacy of BIIB017 in paediatric subjects aged 10 to less than 18 years for the treatment of relapsing remitting multiple sclerosis, with optional open-label extension"

### Description

This was an open-label, randomized, multicenter, active-controlled, parallel-group study of BIIB017 in paediatric participants aged 10 to < 18 years for the treatment of RRMS. After stratification, participants were randomized using interactive voice/web response technology (IXRS) in a 1:1 ratio to treatment with BIIB017 or Avonex for Part 1 of this Study. Participants who were randomized in Part 1 of the study to receive BIIB017, were administered 125 µg subcutaneously (SC) every 2 weeks (Q2W) for 96 weeks. Participants who were randomized to receive Avonex in Part 1 of the study self-administered (or given via a proxy) a dose of 30 µg intramuscular (IM) injection once weekly beginning with the Day 1/Baseline Visit. Participants who completed the study treatment at Week 96 in Part 1 and were eligible for and choose to enrol in Part 2 of the study, will receive BIIB017 for 96 weeks.

### Methods

#### *Study participants*

Patients aged 10 to < 18 years old at the time of informed consent having a diagnosis of RRMS as defined by the revised consensus definition for paediatric multiple sclerosis. They must have had experienced ≥ 1 relapse in the 12 months prior to randomization (Day 1) or ≥ 2 relapses in the 24 months prior to randomization (Day 1) or had evidence of asymptomatic disease activity (Gd-enhancing lesions) on brain magnetic resonance imaging in the 6 months prior to randomization (Day 1).

#### *Treatments*

BIIB017 was taken at a dose of 125 µg SC every 2 weeks for 96 weeks. To mitigate flu-like symptoms, participants were titrated to the target dose of BIIB017 125 µg as follows: BIIB017 63 µg on Day 1, 94 µg at Week 2, and 125 µg at Week 4. Once target dose was reached, participants continued on this dose for the remainder of the study.

Avonex was started at a dose of 7.5 µg and the dose increased by 7.5 µg each week for 3 weeks until the recommended dose of 30 µg was achieved. The purpose of the titration was to reduce the incidence and ameliorate flu-like symptoms that may otherwise had occurred if Avonex therapy was initiated at a dose of 30 µg. Following titration, Avonex was administered once weekly by IM injection according to local prescribing information.

***Duration of Treatment and Follow-Up***

Study duration for each participant participating in Part 1 and Part 2 of the study was to be approximately 200 weeks:

- 4-week screening period
- 96-week treatment period in Part 1 (including a 4-week titration period)
- 96-week treatment period in Part 2 (including a 4-week titration period for participants who switched from Avonex to BIIB017)
- 4-week follow-up period

The follow-up period included a final study visit 4 weeks after the last dose of study treatment.

***Objectives***

The primary objectives are to evaluate the safety, tolerability, and descriptive efficacy of BIIB017 in paediatric participants with RRMS and to assess pharmacokinetics. An exploratory objective is to collect additional efficacy information.

***Outcomes/endpoints***

Primary Endpoint: Annualized relapse rate (ARR) at Week 48

Secondary endpoints related to efficacy:

- ARR at Week 96
- Proportion of participants free of new or newly enlarging T2 hyperintense lesions on brain MRI scans at Weeks 24, 48, and 96
- Proportion of participants free of new MRI activity in the brain (free of Gd-enhancing lesions and new or newly enlarging T2 hyperintense lesions) at Weeks 24, 48, and 96
- Number of new or newly enlarging T2 hyperintense lesions on brain MRI scans at Weeks 24, 48, and 96
- Number of Gd-enhancing lesions on brain MRI scans at Weeks 24, 48, and 96
- Time to first relapse
- Proportion of participants free of relapse up to Weeks 48 and 96
- Change from baseline in cognition as measured by the Symbol Digit Modality Test (SDMT) at Weeks 24, 48, 72, and 96
- Change from baseline in the Expanded Disability Status Scale (EDSS) score at Weeks 48 and 96

- Change from baseline in the quality of life as measured by the Pediatric Quality of Life Inventory (PedsQL) at Weeks 24, 48, 72, and 96

Secondary endpoints related to PK: exposure (area under the plasma concentration-time curve for a dosing interval [AUCtau]), maximum concentration (Cmax) at steady state, and time to reach Cmax (Tmax) at steady state

Secondary endpoints related to safety:

- Incidence of adverse events (AEs), serious AEs (SAEs), and AEs leading to study treatment discontinuation
- Change over time in growth parameters, including height, weight, and Tanner Score (if applicable)
- Immunogenicity as assessed by the development of binding and neutralizing antibodies to IFN β-1a (all participants) and/or binding antibodies to polyethylene glycol (PEG) [BIIB017-treated participants]
- Change from baseline in depression as assessed by Mini International Neuropsychiatric Interview for Children and Adolescents (MINI KID)
- Change from baseline in vital signs and 12-lead electrocardiogram (ECG) parameters
- Change over time in hematology, clinical laboratory values (including liver, renal, and thyroid function), and coagulation

***Sample size***

This study was not powered for the primary efficacy endpoint of Part 1. The sample size was originally primarily based on feasibility, with the goal of having at least 50 evaluable participants at the 2-year (96-week) timepoint of Part 1 in each treatment group.

The original considerations in setting the sample size were based on a projected dropout rate of approximately 30% over a 2-year period, and a total of approximately 142 participants were planned to be randomized to have at least 100 evaluable participants (50 evaluable participants per treatment group) after 2 years (96 weeks) of treatment.

Under the current protocol, the primary analysis was planned to occur once at least 100 evaluable participants, stratified by age, reach Week 48.

***Randomisation and blinding***

This is a randomised study (1:1) and open study (blinding is therefore not applicable).

***Statistical Methods***

Analysis populations were defined as follows:

• Full Analysis Set (FAS), defined as all randomized participants who received at least 1 dose of study treatment in Part 1. Efficacy endpoints were analyzed using the FAS. In analyses performed on the FAS, participants were analyzed, based on the intention-to-treat principle, according to their randomized treatment assignment regardless of treatment received.

• Safety Analysis Set, defined as all randomized participants who received at least 1 dose of study treatment in Part 1, essentially the same set of participants included in the FAS. Safety endpoints were analyzed using the Safety Analysis Set. In analyses performed on the Safety Analysis Set, participants were analyzed according to their actual treatment received.

• Pharmacokinetic Analysis Set, defined as all participants who received at least 1 dose of BIIB017 treatment in Part 1 and have at least 1 measurable drug concentration postbaseline.

• Per Protocol Set, defined as all randomized participants who received at least 1 dose of study treatment and completed 48 weeks of Part 1 without major protocol deviations. These analyses commenced only if there are differences > 10 in any treatment group in number of participants between the Per Protocol Set and FAS. Participants were analyzed according to their randomized treatment assignment regardless of treatment received. The primary endpoint (ARR at Study Week 48) was analyzed in the Per Protocol Set in addition to the FAS.

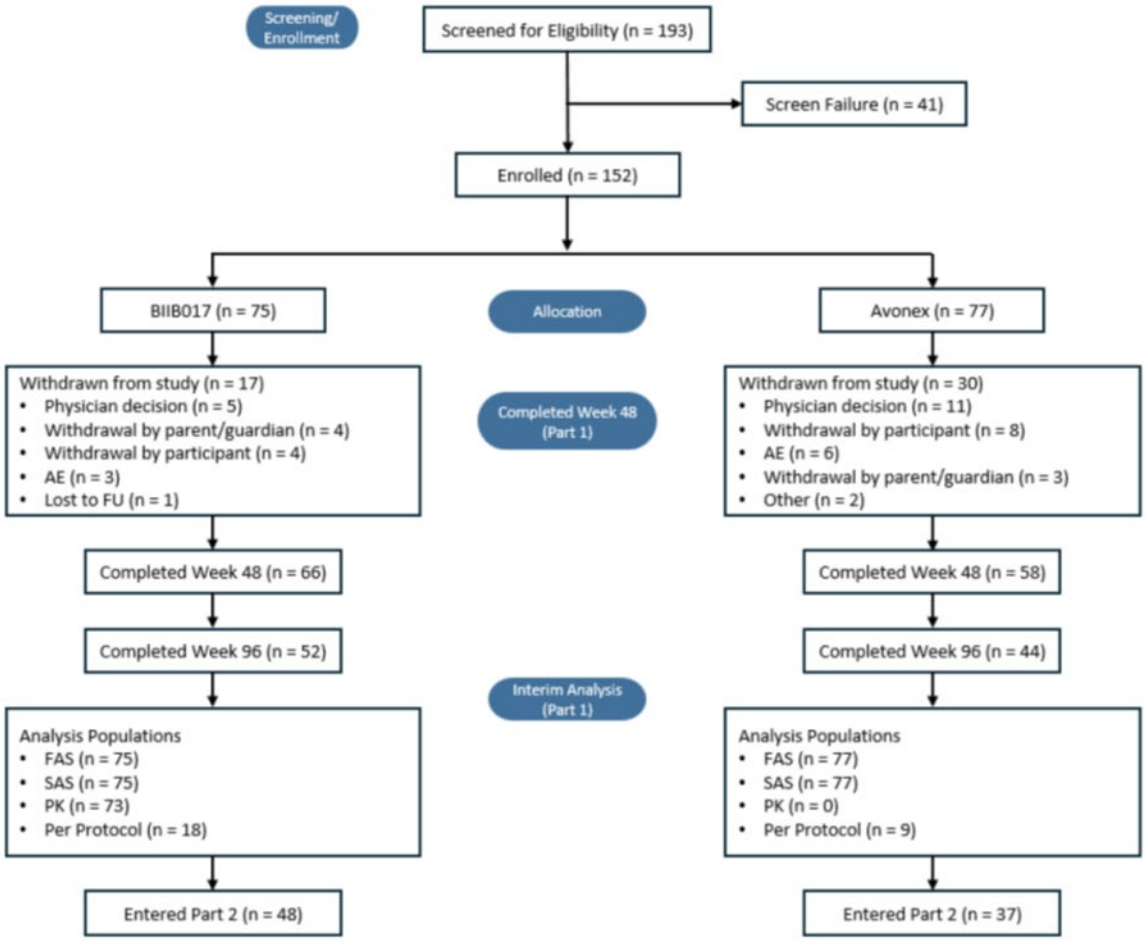
For the purposes of the statistical analyses, analyses based on data collected from all evaluable participants through Week 48 of Part 1, plus any additional data available from later timepoints as applicable (referred to as the Part 1a analysis) will be performed separately from the analysis of data from the entire 96 weeks of treatment in Part 1 plus the 4 weeks of safety follow-up, as applicable (referred to as the Part 1a + 1b analysis). In Part 2 (open-label extension), the long-term safety and MS outcomes of BIIB017 in the paediatric RRMS population will be investigated and reported in the final CSR upon study completion.

Under the current protocol, the primary analysis was planned to occur once at least 100 evaluable participants, stratified by age, reach Week 48.

## Results

### *Participant flow*

Figure 1: CONSORT flow diagram for disposition of participants in part 1 at interim analysis




### *Recruitment*

As of data cutoff date, a total of 152 participants (Avonex group, 77 participants; BIIB017 group, 75 participants) were enrolled in Part 1 of the study and were randomly assigned to treatment and received at least 1 dose of study treatment. There were 124 participants (81.6%) who completed Week 48 of the study: 58 participants (75.3%) in the Avonex group and 66 participants (88.0%) in the BIIB017 group. There were 96 participants (63.2%) who completed Week 96 of the study: 44 participants (57.1%) in the Avonex group and 52 participants (69.3%) in the BIIB017 group. There were 52 participants (34.2%) who discontinued study treatment overall: 33 participants (42.9%) in the Avonex group and 19 participants (25.3%) in the BIIB017 group. Overall, the most common reasons for study treatment discontinuation were physician decision (18 participants [11.8%]), AEs and participant withdrawal (11 participants [7.2%] each), and parent/guardian withdrawal (7 participants [4.6%]). 47 participants (30.9%) were withdrawn from the study overall: 30 participants (30.9%) in the Avonex group and 17 participants (22.7%) in the BIIB017 group. Overall, the most common reasons for withdrawal from the

study were physician decision (16 participants [10.5%]), participant withdrawal (12 participants [7.9%]), AEs (9 participants [5.9%]), and parent/guardian withdrawal (7 participants [4.6%]).

***Baseline data***

Overall, the mean (standard deviation [SD]) age was 15.1 (1.87) years and ages ranged from 10 to 17 years. Approximately two-thirds of the participants were female (95 participants, 62.5%). Most participants were aged 15 to 17 years ([104 participants, 68.4%] and most participants were White (135 participants, 88.8%]). The mean (SD) weight was 64.2 (15.29) kg, and the mean (SD) height was 166.3 (10.36) cm. Demographic characteristics were similar overall in both treatment groups.

Overall, the mean (SD) time since first MS symptoms was 1.2 (1.27) years with a mean (SD) time since diagnosis of 0.7 (1.02) years. Of 152 participants, most participants had only 1 relapse in the past 12 months (92 participants [60.5%]) or 24 months (73 participants [48.0%]). The mean (SD) time since the most recent prestudy relapse was 6.2 (7.25) months. Most participants (137 of 152) had an EDSS score between 0 and 2 at Baseline.

***Number analysed***

The target sample size was 142 participants. 152 participants were analysed.

***Efficacy results***

There is no specific discussion on the efficacy of Avonex.

At Week 48, the adjusted ARR (95% CI) was 0.521 (0.322, 0.843) in the Avonex group and 0.386 (0.231, 0.646) in the BIIB017 group. The mean (SD) participant relapse rate was 0.81 (1.994) in the Avonex group and 0.40 (0.907) in the BIIB017 group. At Week 98, the adjusted ARR (95% CI) was 0.526 (0.341, 0.812) in the Avonex group and 0.291 (0.177, 0.479) in the BIIB017 group. The mean (SD) participant relapse rate was 0.82 (1.951) in the Avonex group and 0.34 (0.798) in the BIIB017 group.

There were 32 participants (41.6%) in the Avonex group and 21 participants (28.0%) in the BIIB017 group who experienced a relapse. The number and percentage of participants who did not have a relapse regardless of time in the study was 45 (58.4%) in the Avonex group and 54 (72.0%) in the BIIB017 group. The estimated proportion of participants who were relapse-free at Week 48 was 0.662 in the Avonex group and 0.764 in the BIIB017 group; at Week 72 was 0.613 in the Avonex group and 0.718 in the BIIB017 group; and at Week 96 was 0.531 in the Avonex group and 0.718 in the BIIB017 group.

MRI efficacy analyses results were similar in both Avonex and BIIB017 groups.

Overall, the SDMT and EDSS scores remained consistent over the course of the study through Week 96, with minimal change from baseline over the assessment timepoints. The mean PedsQL scale scores across all 5 dimensions were similar between Avonex and BIIB017 treatment groups, with mean scores within 1 SD, except for the Work/School dimension.

***Safety results***

There is no specific discussion on the safety of Avonex.

The safety analyses were performed using the safety analysis set (all randomized participants who received at least 1 dose of study treatment in Part 1 and were analyzed according to their actual

treatment received). Results presented are for Part 1 through Week 48 of the study including all available data collected for the remainder of Part 1 (through Week 96).

Patient exposure

Overall, the mean (SD) duration of exposure to study treatment as of the data cut off date was 75.5 (28.86) weeks and the median was 94.3 weeks. Overall, the exposure bracket with the highest number of participants (68 of 152 [45%]) exposed to study treatment was > 88 weeks to ≤ 96 weeks. The exposure bracket with the second highest number of participants (22 of 152 [14%]) exposed to study treatment was > 96 weeks.

**Adverse Events**

Overall, TEAEs were reported for 129 of 152 participants (84.9%). TEAEs were reported in a similar percentage of participants in both treatment groups (Avonex group: 63 participants, 81.8%; BIIB017: 66 participants, 88.0%). By PT, the most common TEAEs (reported in > 10% of participants) were multiple sclerosis relapse (50 participants [32.9%]), influenza like illness (41 participants [27.0%]), injection site erythema (31 participants [20.4%]), headache (30 participants [19.7%]), and pyrexia (22 participants [14.5%]). Of these, the largest between-group difference was for injection site erythema: 6 participants (7.8%) in the Avonex group and 25 participants (33.3%) in the BIIB017 group; followed by multiple sclerosis relapse: 30 participants (39.0%) in the Avonex group and 20 participants (26.7%) in the BIIB017 group. Overall, in the safety analysis set, 94 participants (61.8%) had TEAEs that were considered by the Investigator related to study treatment. The percentage of participants who had TEAEs that were related to study treatment was similar in both the Avonex group (45 participants [58.4%]) and BIIB017 group (49 participants [65.3%]). By PT, related TEAEs experienced by ≥ 20% participants overall were influenza like illness (41 participants [27.0%]) and injection site erythema (31 participants [20.4%]). The related TEAE of influenza like illness was reported for 25 participants (32.5%) in the Avonex group and 16 participants (21.3%) in the BIIB017 group. The related TEAE of injection site erythema was reported for 6 participants (7.8%) in the Avonex group and 25 participants (33.3%) in the BIIB017 group.

Serious adverse events

By PT, treatment-emergent SAEs experienced by ≥ 2 participants overall were multiple sclerosis relapse (15 participants [9.9%]) and complicated appendicitis (2 participants [1.3%]). The SAE of multiple sclerosis relapse was reported for 11 participants (14.3%) in the Avonex group and 4 participants (5.3%) in the BIIB017 group. The SAE of complicated appendicitis was reported only in Avonex group (2 participants [2.6%]) and considered by the investigator unrelated to the study treatment in both cases.

The Investigator considered the following treatment-emergent SAEs related to study treatment: abdominal pain, haematuria, and hemorrhagic ovarian cyst (1 participant [0.7%] each], all occurred in the Avonex group).

Adverse events leading to discontinuation

TEAEs that led to discontinuation of study treatment in > 1 participant were multiple sclerosis relapse and suicidal ideation (2 participants [1.3%] each). Multiple sclerosis relapse was reported for 1 participant (1.3%) in each group. Suicidal ideation was reported for 2 participants (2.6%) in the Avonex group and 0 participants in the BIIB017 group. In both cases, the Investigator assessed the intensity of the event of suicidal ideation as severe and considered the event to be related to the study treatment.

Additionally, one AE (multiple sclerosis relapse) in each study arm (1 participant in the Avonex group and 1 participant in the BIIB017 group) were classified as not treatment-emergent because they occurred during the follow-up period (i.e., after the discontinuation of the study drug)

**Clinical laboratory evaluations**

Hematology Results

The parameters in which a shift from baseline normal, high, or unknown values to low values occurred in ≥ 25.0% of participants in either treatment group were the following: leukocyte count (15 of 73 participants [20.5%] in the Avonex group and 43 of 71 participants [60.6%] in the BIIB017 group); neutrophil count (16 of 71 participants [22.5%] in the Avonex group and 43 of 74 participants [58.1%] in the BIIB017 group); neutrophils/leukocytes (14 of 70 participants [20.0%] in the Avonex group and 26 of 74 participants [35.1%] in the BIIB017 group); and haematocrit (7 of 73 participants [9.6%] in the Avonex group and 18 of 70 participants [25.7%] in the BIIB017 group).

The parameters in which a shift from baseline normal, high, or unknown values to low values occurred in ≥ 25.0% of participants in either treatment group were the following: leukocyte count (15 of 73 participants [20.5%] in the Avonex group and 43 of 71 participants [60.6%] in the BIIB017 group); neutrophil count (16 of 71 participants [22.5%] in the Avonex group and 43 of 74 participants [58.1%] in the BIIB017 group); neutrophils/leukocytes (14 of 70 participants [20.0%] in the Avonex group and 26 of 74 participants [35.1%] in the BIIB017 group); and haematocrit (7 of 73 participants [9.6%] in the Avonex group and 18 of 70 participants [25.7%] in the BIIB017 group).

The parameters in which a shift from baseline normal, low, or unknown values to high values occurred in ≥ 25.0% of participants in either treatment group were the following: lymphocytes/leukocytes (18 of 73 participants [24.7%] in the Avonex group and 28 of 74 participants [37.8%] in the BIIB017 group); basophils/leukocytes (22 of 61 participants [36.1%] in the Avonex group and 17 of 58 participants [29.3%] in the BIIB017 group); basophil count (21 of 70 participants [30.0%] in the Avonex group and 11 of 67 participants [16.4%] in the BIIB017 group); monocytes/leukocytes (21 of 71 participants [29.6%] in the Avonex group and 20 of 70 participants [28.6%] in the BIIB017 group); and eosinophils/leukocytes (13 of 62 participants [21.0%] %] in the Avonex group and 16 of 61 participants [26.2%] in the BIIB017 group).

As of the data cutoff date, 8 participants had lymphocyte counts < lower limit of normal (LLN), 5 participants in the Avonex group and 3 participants in the BIIB017 group. All 8 participants had post-baseline lymphocyte counts < LLN; at some visits the lymphocyte counts were < 0.9 × 109/L. All 8 participants completed the study and did not enter the long-term extension study.

Blood Chemistry Results

Abnormal ALT and AST values were reported in following categories: > 1 to < 3 upper limit of normal (ULN), ≥ 3 to 5 × ULN, > 5 to 10 × ULN, > 10 to 20 × ULN, and > 20 × ULN. However, none of the participants had laboratory results that met Hy's law criteria.

No parameters shifted to low values in ≥ 25.0% of participants in either treatment group. Overall, 46 of 135 participants (34.1%) had a shift to high phosphate concentrations from baseline (22 of 68 participants [32.4%] in the Avonex group and 24 of 67 participants [35.8%] in the BIIB017 group), 47 of 139 participants (33.8%) had a shift to high ALT concentration (20 of 70 participants [28.6%] in the Avonex group and 27 of 69 participants [39.1%] in the BIIB017 group), 42 of 141 participants (29.8%) had a shift to high glucose concentrations (27 of 70 participants [38.6%] in the Avonex group and 15 of

71 participants [21.1%] in the BIIB017 group), and 33 of 148 participants (22.3%) had a shift to high AST concentration (11 of 74 participants [14.9%] in the Avonex group and 22 of 74 participants [29.7%] in the BIIB017 group)

Thyroid Stimulating Hormone Results

One participant in Avonex group had an AE of blood thyroid stimulating hormone decreased which was not related to the study drug and the participant recovered from the event. Another participant had an adverse event of blood thyroid stimulating hormone increased which was not related to study drug and the participant recovered from this event.

**Vital signs measurements, physical examination findings, and other observation related to safety.**

Vital Sign Measurements

The most common clinically relevant vital sign abnormality (reported in > 10% of participants overall) was high pulse rate (> 120 bpm postbaseline or an increase from baseline of > 20 bpm) in 24 of 151 participants (15.9%) and a low pulse rate (< 50 bpm or > 20 bpm decrease from baseline) in 19 of 151 participants (12.6%).Except for low pulse rate (12 of 77 participants [15.6%] in the Avonex group and 7 of 74 participants [9.5%] in the BIIB017 group) and low systolic blood pressure (0 of 77 participants in the Avonex group and 5 of 74 participants [6.8%] in the BIIB017 group), the percentages of participants experiencing each type of clinically relevant abnormality were generally similar in both treatment groups.

ECGs

Overall, 11 of 133 participants (8.3%) experienced a shift to abnormal in their ECG results (6 of 67 participants [9.0%] in the Avonex group and 5 of 66 participants [7.6%] in the BIIB017 group). There were no adverse events associated with ECG shifts.

Immunogenicity Assessments

Overall, 150 participants were included in this analysis (75 participants each in the Avonex and BIIB017 groups). Of these participants, 57 (38.0%) tested positive for anti-IFN-β-1a antibodies (28 participants [37.3%] in the Avonex group and 29 participants [38.7%] in the BIIB017 group) and 15 participants (10.1%) tested positive for neutralizing IFN-β-1a antibodies (13 participants [17.3%] in the Avonex group and 2 participants [2.7%] in the BIIB017 group). The incidence of participants with neutralizing IFN-β-1a antibodies in the BIIB017 group was low and nonpersistent. There was no apparent impact on safety or clinical efficacy, although the analysis was limited by the low incidence of immunogenicity. Anti-PEG antibodies were present at Baseline in 92% of participants and were persistent during the study in participants taking BIIB017. Avonex participants were not tested for anti-PEG antibodies as Avonex is not pegylated.

## 2.3.3. Discussion on clinical aspects

The MAH has not provided a discussion on the efficacy or safety of Avonex. Study 105MS306 is not designed to conclude on efficacy of Avonex.

With respect to the primary efficacy outcome, ARR at Week 48, the mean participant relapse rate in both the FAS and PP set was lower in the BIIB017 group than in the Avonex group. The secondary efficacy endpoints indicated that at Week 96, the mean (SD) participant relapse rate was lower in BIIB017 group

than in the Avonex group. Time to first relapse was higher in participants in the BIIB017 group compared to the Avonex group. The proportion of participants who did not have a relapse regardless of time in the study and who were relapse-free was higher in the BIIB017 group than in the Avonex group. MRI efficacy analyses results were similar in both Avonex and BIIB017 groups. Overall, the SDMT and EDSS scores remained consistent over the course of the study through Week 96, with minimal change from baseline over the assessment timepoints. The mean PedsQL scale scores across all 5 dimensions were similar between Avonex and BIIB017 treatment groups, with mean scores within 1 SD, except for the Work/School dimension.

Regarding safety, overall, the incidence and type of AEs observed were consistent with those of adults. Of interest, suicidal ideation was reported for 2 participants (2.6%) in the Avonex group leading to discontinuation of study treatment. In both cases, the Investigator assessed the intensity of the event of suicidal ideation as severe and considered the event to be related to the study treatment.

# 3. CHMP's overall conclusion and recommendation

The MAH has submitted an interim report for Study 105MS306, "*An Open-label, randomized, multicenter, active-controlled, parallel-group study to evaluate the safety, tolerability and efficacy of BIIB017 in paediatric subjects aged 10 to less than 18 years for the treatment of relapsing remitting multiple sclerosis, with optional open-label extension*". This interim clinical study report provides the results for part 1 of the study through week 48, referred to as the part 1a analysis.

This study is part of the agreed paediatric investigation plan for peginterferon beta-1a (EMEA-001129-PIP01-M06). The same report has been submitted by the MAH for Plegridy (peginterferon beta-1a; BIIB017). Only part 1a of the study 105MS306 (treatment period through week 48) is part of the PIP, this might be the reason for the submission of an interim report as an obligation in accordance to Article 46 of Regulation (EC) No1901/2006. For the present procedure the relevant data are those from Avonex, used as a comparator in the study.

The MAH has not provided a discussion on the efficacy or safety of Avonex.

Study 105MS306 is not designed to conclude on efficacy of Avonex. With respect to the primary efficacy outcome, ARR at Week 48, the mean participant relapse rate in both the FAS and PP set was lower in the BIIB017 group than in the Avonex group.

Regarding safety, overall, the incidence and type of AEs observed were consistent with those of adults. Of interest, suicidal ideation was reported for 2 patients (2.6%) in the Avonex group leading to discontinuation of study treatment. In both cases, the investigator assessed the intensity of the event of suicidal ideation as severe and considered the event to be related to the study treatment. Special warnings are already included in the summary of product characteristics referring symptoms of depression and suicidal ideation: "*AVONEX should be administered with caution to patients with previous or current depressive disorders in particular to those with antecedents of suicidal ideation (see section 4.3). Depression and suicidal ideation are known to occur in increased frequency in the multiple sclerosis population and in association with interferon use. Patients treated with AVONEX should be advised to immediately report any symptoms of depression and/or suicidal ideation to their prescribing physician. Patients exhibiting depression should be monitored closely during therapy with AVONEX and treated appropriately. Cessation of therapy with Avonex should be considered (see also sections 4.3 and 4.8)*." In section 4.8, suicide is included in the table listing adverse reactions with a frequency that is unknown. It could be considered to specifically mentioned the adverse reaction of suicidal ideation under the subheading Paediatric population in this section.

Avonex is not approved for the treatment of paediatric patients with multiple sclerosis. There have been no formal clinical studies to assess the efficacy of interferon beta-1a in this population. However, the SmPC was recently modified to include data from studies in which Avonex was used as a control along with postmarketing data from Biogen global safety database and data from published literature. Sections 4.1, 4.2, 4.8 and 5.1 of the SmPC were updated. Although a firm recommendation on posology was not possible, the modification is considered helpful for prescribers. In a similar way, the MAH may consider to make a new proposal, mainly for sections 4.8 and 5.1, where a short description of the now submitted study could be made referring to the design, the study population with numbers of treated patients, the dosage and treatment regimen, the study duration and the results for the main efficacy endpoints (section 5.1 Plegridy SmPC can be used as a guide).

## Fulfilled:

No further action is required, however additional data are expected in the context of a variation before any conclusion on product information amendments is made.