16 April 2026
EMADOC-1700519818-2791881
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Avonex

International non-proprietary name: Interferon beta-1A

Procedure No. EMA/VR/0000320809

Note

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

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List of abbreviations

AE: adverse event
ALT: alanine aminotransferase
ARR: annualized relapse rate
AST: aspartate aminotransferase
AUC0-tau: area under the plasma concentration-time curve for a dosing interval
CI confidence interval
CL/F total clearance
Cmax: maximum concentration
Ctrough: trough concentration
CSR: clinical study report
ECG: electrocardiogram
EDSS: Expanded Disability Status Scale
EU: European Union
FAS: full analysis set
FU: follow up
IFN interferon
IFN α interferon alpha
IFN β interferon beta
IFN β-1a interferon beta type 1a
IM intramuscular
IXRS: interactive voice/web response technology
LLN: lower limit of normal
LS: least squares
MAH: Marketing Authorization Holder
MINI: Mini International Neuropsychiatric Interview
MINI-KID: Mini International Neuropsychiatric Interview for Children and Adolescents
MRI: magnetic resonance imaging
MS: multiple sclerosis
PedsQL: Pediatric Quality of Life Inventory™
PEG: polyethylene glycol
PFS: prefilled syringe
PK: pharmacokinetics
PT: preferred term
Q2W: every 2 weeks
RBC: red blood cell
RRMS: relapsing-remitting multiple sclerosis
SAE: serious adverse event
SC: subcutaneous(ly)
SD: standard deviation
SDMT: Symbol Digit Modality Test
SOC: system organ class
TEAE: treatment-emergent adverse event
Tmax: time to reach maximum concentration
ULN: upper limit of normal

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Biogen Netherlands B.V. submitted to the European Medicines Agency on 19 December 2025 an application for a variation.

The following changes were proposed:

Variation(s) requested		Type
C.I.3.b	C.I.3.b Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH	Variation type II

Update of section 5.1 of the SmPC following the outcome of procedure P46 PAM/0000245472, based on interim results from study 105MS306 (CHARGE). This is 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.

The requested variation(s) proposed amendments to the Summary of Product Characteristics.

2. Overall conclusion and impact on the benefit/risk balance

On 13 January 2025, the MAH submitted an interim report of Study 105MS306 (CHARGE), a paediatric study for Avonex, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, based on interim data (Part 1- week 48). Now the applicant is applying for a single Type II variation to update Avonex Product Information based on interim (Part 1 - week 96) Clinical Study Report of study 105MS306 (dated 15 December 2025).

Study 105MS306 (CHARGE) is an open-label, randomized, multicenter active-controlled, parallel-group study, with an ongoing optional open-label extension (Part 2). Part 1 of the study was conducted to evaluate the safety, tolerability, descriptive efficacy, and pharmacokinetic of BIIB017 (peginterferon beta-1a; PLEGRIDY, 125 µg SC administered every 2 weeks) in paediatric subjects aged 10 to < 18 years with the active control Avonex (IFN β-1a, 30 µg once weekly by IM injection). The first participant in Part 1 was treated on 18 October 2019, and the data cut-off date for this analysis of Part 1 (Week 96) of the study was 18 June 2025.

Study 105MS306 is part of the agreed paediatric investigation plan for peginterferon beta-1a (EMEA-001129-PIP01-M06). It is not designed to conclude on efficacy of Avonex.

Additional treatment data for Avonex is available from a recently published observational study [Wright 2025]: Evaluating efficacy outcomes in paediatric MS patients while using Avonex or Plegridy via the United States Network of Pediatric Multiple Sclerosis Centers registry.

Overall conclusion has not changed with respect to the previous assessment (part 1-week 48; EMA/PAM/000024547). In terms of efficacy, although no statistically significant differences were observed between BIIB017 and Avonex, numerical trends in favour of BIIB017 were observed across a range of clinical and MRI endpoints. In the Avonex group, the mean relapse rate at Week 48 was numerically higher compared with BIIB017 in both the FAS and Per Protocol populations. Secondary efficacy outcomes through Week 96 numerically favoured BIIB017, with numerically lower values across a range of endpoints: relapse rates, time to first relapse, and proportion of relapse-free participants relative to Avonex. MRI analyses demonstrated numerical differences favouring BIIB017 over Avonex. Measures of disability and cognition (EDSS, SDMT) remained stable across both treatment groups, and quality of life outcomes were generally comparable, with only minor differences

observed in the Work/School domain.

Regarding safety, overall, the incidence and type of AEs observed were consistent with those of adults. 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. Contraindication (4.3) and Special warnings and precaution for use (4.4) in the SmPC already reflect the concerns in relation to the use of Avonex in patients with current severe depression and/or suicidal ideation and the precautions to be followed: "*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)*." Also in section 4.8, suicide is included in the table listing adverse reactions with a frequency that is unknown. The MAH has not considered to specifically mention the adverse reaction of suicidal ideation under the subheading Paediatric population in this section.

As a result of this variation application, section 5.1 of the SmPC is being updated. Please, refer to the PI for further information.

The benefit-risk balance of Avonex remains positive.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation(s) requested		**Type**
C.I.3.b	C.I.3.b Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH	Variation type II

Update of section 5.1 of the SmPC following the outcome of procedure P46 PAM/0000245472, based on interim results from study 105MS306 (CHARGE). This is 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.

☒ is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex I are recommended.

4. EPAR changes

The table in the 'Steps after' module of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Avonex-H-C-000102-II-EMA/VR/0000320809'.

For more information, please refer to the Summary of Product Characteristics.

Annex: Rapporteur’s assessment comments on the type II variation

5. Introduction

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 has previously been updated to include data from studies in which Avonex was used as a control.

On January 2025, 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 (RRMS), with optional open-label extension". This first interim clinical study report provided the interim analysis results for part 1 of the study through week 48, referred to as the part 1a analysis. On March 2025, a final assessment report for this procedure (Art. 46 PAM procedure - EMA/PAM/0000245472) was issued, but it was agreed that data derived from this assessment would be included in the SmPC once the second interim report was ready. Variation was postponed until a future date.

An application for a single Type II variation to update Avonex product information is now submitted (dated 15 December 2025) based on interim results for part 1 of the study 105MS306 (CHARGE) through week 96.

Additionally, following outcome of procedure EMA/PAM/0000245472, the MAH found minor errors in the interim CSRs (week 48 and week 96). The errata for both CSRs are included in this submission. The MAH confirmed that these changes do not impact the safety of study participants and interpretation of study results and conclusions. An addendum to the Clinical Overview of the efficacy and safety data from Study 105MS306 part 1 (through week 96, data cut-off date of 18 June 2025) was submitted with the purpose of presenting information that supports an update to the Avonex EU PI. This update is made to implement the outcome of assessment of procedure EMA/PAM/0000245472, to include key data from Study 105MS306.

Study 105MS306 (CHARGE) is an open-label, randomized, multicenter active-controlled, parallel-group study, with an ongoing optional open-label extension (Part 2). Part 1 of the study was conducted to evaluate the safety, tolerability, descriptive efficacy, and pharmacokinetic of BIIB017 (peginterferon beta-1a; PLEGRIDY®, 125 µg SC administered every 2 weeks) in paediatric subjects aged 10 to < 18 years with the active control Avonex (IFN β-1a, 30 µg once weekly by IM injection). The first participant in Part 1 was treated on 18 October 2019, and the data cut-off date for this analysis of Part 1 (Week 96) of the study was 18 June 2025.

6. Clinical Pharmacology aspects

Not applicable.

7. Clinical Efficacy aspects

Study 105MS306 Part 1 assessed the efficacy of BIIB017 with Avonex as the active comparator in paediatric participants with RRMS when the last participant completed the Week 96 treatment of the study.

Description

7.1. Methods – analysis of data submitted

Study Population

The participants included in this ongoing study were ages 10 to <18 years with a diagnosis of RRMS, an EDSS score between 0.0 and 5.5 at randomisation (Day 1), and 1 of the following additional criteria: ≥ 1 relapse in the 12 months prior to randomisation (Day 1); ≥ 2 relapses in the 24 months prior to randomisation (Day 1); or evidence of asymptomatic disease activity (Gd enhancing lesions) on brain MRI in the 6 months prior to randomisation (Day 1).

Participants were randomised in a 1:1 ratio to receive treatment with either BIIB017 (125 µg SC administered every 2 weeks) or Avonex (30 µg IM once weekly). Participants were males (n = 57) and females (n = 95) with a mean (SD) age of 15.1 (1.87) years in the range of 10 to 17 years. Out of the 152 participants randomised, 15 participants were 10 to 12 years of age, 33 participants were 13 to 14 years of age, and 104 participants were 15 to 17 years of age (CSR 105MS306). This study was not powered for the primary efficacy endpoint of Part 1. The sample size was primarily based on feasibility.

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, defined as the number of relapses during the study period divided by the number of subject-years followed in the study.

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.

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.

7.2. Results

Recruitment

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. As of the data cut-off date, 105 participants (69.1%) completed Week 96 of the study; 47 participants (61.0%) in the Avonex group and 58 participants (77.3%) in the BIIB017 group.

A total of 52 participants (34.2%) discontinued study treatment overall: 33 participants (42.9%) in the Avonex group and 19 participants (25.3%) in the BIIB017 group. The most common reasons for study treatment discontinuation were physician decision (21 participants [13.8%]), AEs and participant withdrawal (11 participants [7.2%] each), and parent/guardian withdrawal (7 participants [4.6%]).

Overall, 47 participants (30.9%) were withdrawn from the study; 30 participants (39.0%) in the Avonex group and 17 participants (22.7%) in the BIIB017 group. The most common reasons for withdrawal from the study included 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%]) (CSR 105MS306).

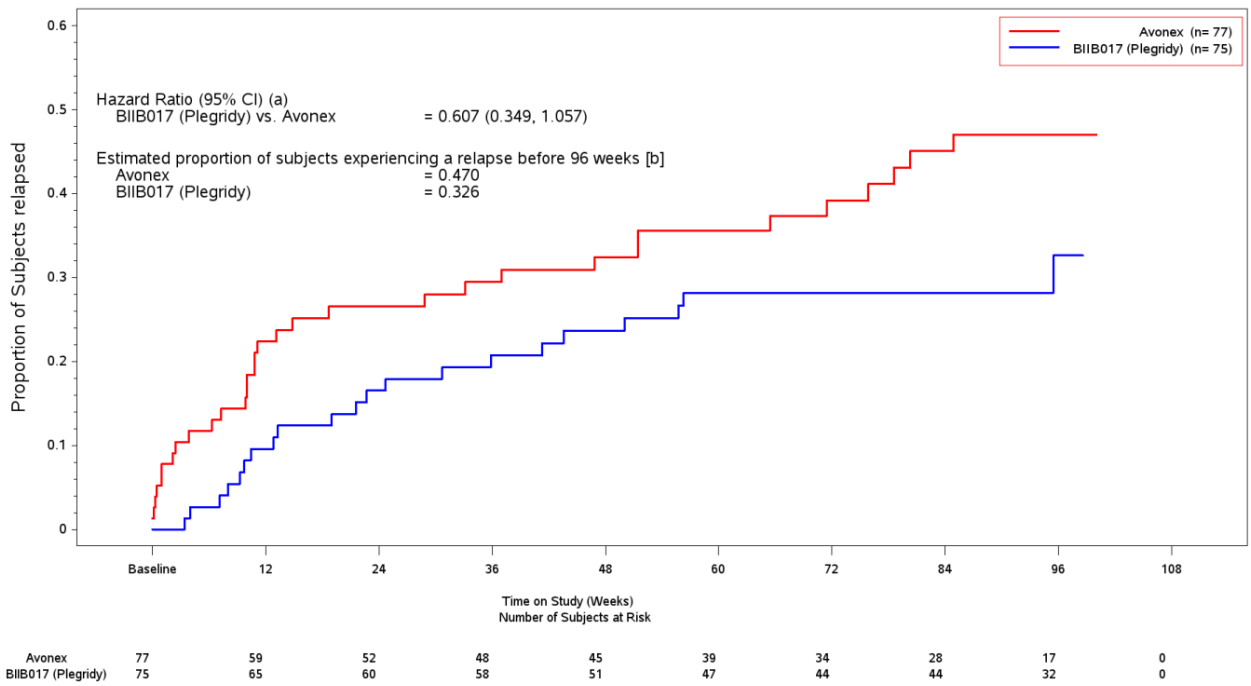
Efficacy Results

In the FAS overall, 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. Overall, the mean (SD) participant relapse rate was 0.61 (1.564). The mean (SD) participant relapse rate was 0.81 (1.994) in the Avonex group compared to 0.40 (0.907) in the BIIB017 group. Results were similar in the Per Protocol Set.

At week 96 the adjusted ARR (95% CI) was 0.527 (0.340, 0.816) in the Avonex group and 0.285 (0.172, 0.471) in the BIIB017 group. Overall, the mean (SD) participant relapse rate was 0.58 (1.513). The mean (SD) participant relapse rate was 0.82 (1.953) in the Avonex group compared to 0.34 (0.798) in the BIIB017 group.

Time to first relapse data is displayed graphically in Figure 1. The number and percentage of participants who did not have a relapse regardless of time in the study was 99 (65.1%) overall: 45 participants (58.4%) in the Avonex group and 54 participants (72.0%) in the BIIB017 group. The estimated Kaplan-Meier proportion of participants who were relapse free at Week 48 was 0.719 overall, 0.676 in the Avonex group, and 0.764 in the BIIB017 group. At Week 72, the estimated proportions were 0.672 overall, 0.627 in the Avonex group, and 0.719 in the BIIB017 group. At Week 96, the estimated proportions were 0.628 overall, 0.530 in the Avonex group, and 0.719 in the BIIB017 group.

Figure 1. Time to First Relapse – Full Analysis Set



NOTE: Time to first protocol-defined relapse.
(a) Based on a Cox proportional hazards model, adjusted for baseline relapse rate (the number of relapses in the 2 years prior to the study, divided by 2), age group and baseline EDSS.
(b) Based on Kaplan-Meier product-limit method.

The overall proportion of participants free of new or newly enlarging T2 hyperintense lesions at Week 96 relative to baseline was 0.105 (95% CI: 0.053, 0.180): 2 of 49 participants in the Avonex group (0.041; 95% CI: 0.005, 0.140) and 9 of 56 participants in the BIIB017 group (0.161; 95% CI: 0.076, 0.283).

The adjusted mean (95% CI) number of new or newly enlarged T2 hyperintense lesions relative to baseline at Week 24 was 11.59 (95% CI: 8.40, 15.99) in the Avonex group and 11.86 (95% CI: 8.55, 16.45) in the BIIB017 group, at Week 48 was 15.25 (95% CI: 10.79, 21.55) in the Avonex group and 17.76 (95% CI: 12.86, 24.53) in the BIIB017 group, and at Week 96 was 20.51 (95% CI: 14.07; 29.90) in the Avonex group and 18.19 (95% CI: 12.63, 26.79) in the BIIB017 group.

At Week 24, of 141 participants with postbaseline MRI scans, the overall mean (SD) number of Gd enhancing lesions was 1.4 (4.82): 1.7 (6.42) in the Avonex group and 1.1 (2.25) in the BIIB017 group. At Week 48, of 128 participants with postbaseline MRI scans, the overall mean (SD) number of Gd enhancing lesions was 0.9 (3.17): 1.3 (4.23) in the Avonex group and 0.5 (1.59) in the BIIB017 group. At Week 96, of 106 participants with postbaseline MRI scans, the overall mean (SD) number of Gd-enhancing lesions was 0.5 (1.30): 0.6 (1.55) in the Avonex group and 0.4 (1.05) in the BIIB017 group.

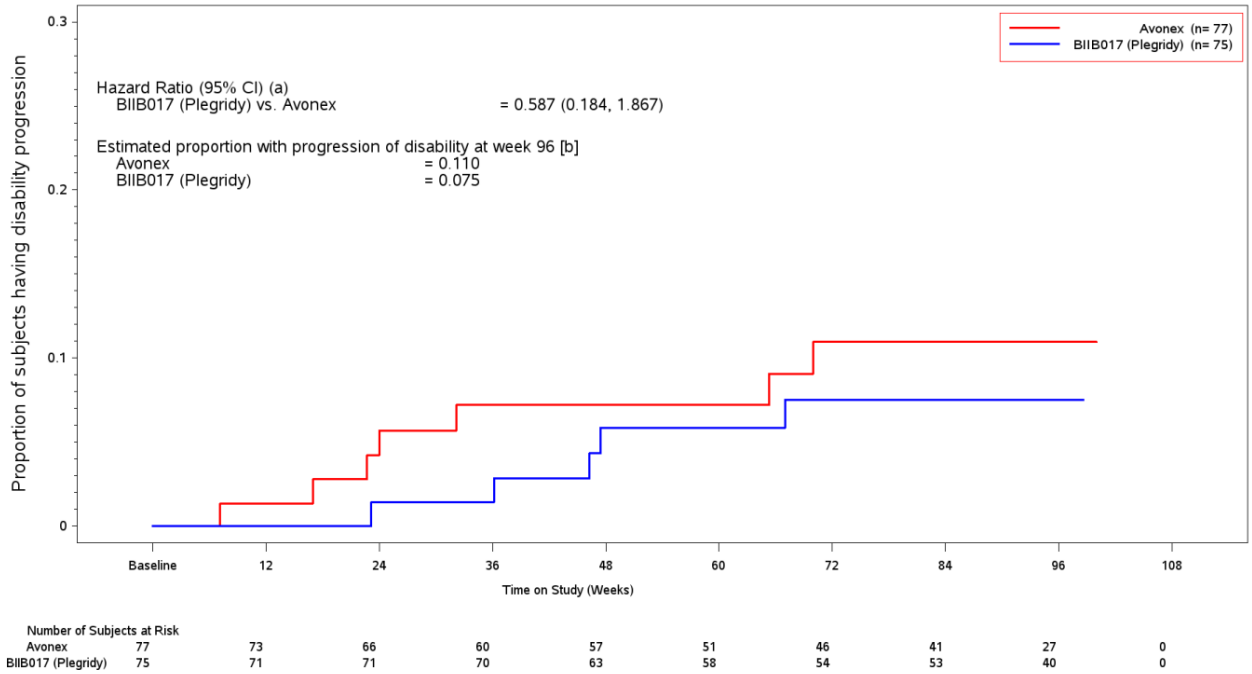
Cognitive ability was assessed by the SDMT conducted at Baseline and every 24 weeks throughout the study. At Week 48, the mean (SD) change from baseline in SDMT score was 4.5 (8.75) in the Avonex group and 1.3 (8.51) in the BIIB017 group. At Week 96, the mean change from baseline in SDMT score was 7.9 (11.64) in the Avonex group and 3.5 (9.67) in the BIIB017 group.

Participants' level of functioning was assessed by the EDSS score conducted at baseline and every 12 weeks throughout the study. At Week 48, the mean (SD) change from baseline in EDSS score was -0.1 (0.70) in the Avonex group and 0.1 (0.64) in the BIIB017 group. At Week 96, the mean change from baseline in EDSS score was 0.0 (0.74) in the Avonex group and 0.1 (0.67) in the BIIB017 group.

Pediatric Quality of Life Inventory™ scale scores were determined every 24 weeks, starting at Baseline. Overall, mean scores in each dimension were similar between Avonex and BIIB017 treatment groups, except for the Work/School dimension.

For the exploratory endpoints, progression of disability occurred in 7 participants (9.1%) in the Avonex group and 5 participants (6.7%) in the BIIB017 group. The estimated proportion of participants with disability progression at Week 24 was 0.042 in the Avonex group and 0.014 in the BIIB017 group; at Week 48, was 0.072 in the Avonex group and 0.043 in the BIIB017 group; and at Week 96, was 0.110 in the Avonex group and 0.075 in the BIIB017 group. The hazard ratio (BIIB017/Avonex) for time to progression of disability based on Cox proportional hazards model, adjusted for baseline EDSS score and age group, was 0.587 (95% CI: 0.184, 1.867). Time to disease progression data are displayed in Figure 2.

Figure 2. Time to 12-week Disability Progression – Full Analysis Set



(a) Hazard ratio is based on a Cox proportional hazards regression model with adjustments for the baseline EDSS and age-group at enrollment.
(b) Based on Kaplan-Meier product-limit method.

The adjusted mean number of new unenhancing T1 hypointense lesions at Week 24 relative to previous MRI was 1.71 (95% CI: 1.05, 2.79) in the Avonex group and 2.42 (95% CI: 1.50, 3.90) in the BIIB017 group. At Week 48, the adjusted mean number of lesions was 1.05 (95% CI: 0.58, 1.91) in the Avonex group and 1.58 (95% CI: 0.89, 2.79) in the BIIB017 group. At Week 96, the adjusted mean number of lesions was 1.03 (95% CI: 0.49, 2.15) in the Avonex group and 1.02 (95% CI: 0.51, 2.08) in the BIIB017 group.

The cumulative number of new unenhancing T1 hypointense lesions at Week 96 was 3.74 (95% CI: 2.23, 6.26) in the Avonex group and 4.14 (95% CI: 2.50, 6.87) in the BIIB017 group.

7.3. Discussion

Study 105MS306 is not designed to conclude on efficacy of Avonex.

Although no statistically significant differences were observed between BIIB017 (Plegridy) and Avonex, numerical trends in favour of BIIB017 were observed across a range of clinical and MRI endpoints. In the Avonex group, the mean relapse rate at Week 48 was numerically higher compared with BIIB017 in both the FAS and Per Protocol populations. Secondary efficacy outcomes through Week 96 numerically favoured BIIB017, with numerically lower values across a range of endpoints: relapse rates, time to first relapse, and proportion of relapse-free participants relative to Avonex. MRI analyses (new or newly enlarged T2 hyperintense lesions and Gd-enhancing lesions on brain MRI) demonstrated numerical differences favouring BIIB017 over Avonex. Measures of disability and cognition (EDSS, SDMT) remained stable across both treatment groups, and quality of life outcomes were generally comparable, with only minor differences observed in the Work/School domain.

Key data from Study 105MS306 has been added to SmPC section 5.1 (Pharmacodynamic properties) of the Avonex EU PI (see section 10).

8. Clinical Safety aspects

8.1. Methods – analysis of data submitted

The safety analyses for Study 105MS306 were performed using the safety analysis set, which included all randomized participants who received at least 1 dose of study treatment in Part 1 and were analysed according to their actual treatment received.

8.2. Results

Patient exposure

Overall, the mean (SD) duration of exposure to study treatment as of the data cut-off date was 76.78 (29.02) weeks and the median was 94.57 weeks. Overall, the exposure bracket with the highest number of participants (79 of 152 [52.0%]) exposed to study treatment was > 84 weeks to ≤ 96 weeks. The exposure bracket with the second highest number of participants (21 of 152 [13.8%]) exposed to study treatment was > 96 weeks.

Overall, the mean (SD) percentage of study treatment taken was 93.27 (11.23%).

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.

Demographic and Other Characteristics of Study Population

Overall, the mean (SD) age was 15.1 (1.87) years and ages ranged from 10 to 17 years. Most participants were aged 15 to 17 years (104 participants, 68.4%). Approximately two-thirds of the participants were female (95 participants, 62.5%) and most participants were White (135 participants, 88.8%) and not Hispanic or Latino (136 participants, 89.5%). The mean (SD) weight was 64.2 (15.29) kg, the mean (SD) height was 166.3 (10.36) cm, and the mean (SD) BMI was 23.1 (4.58) kg/m2. Demographic characteristics were overall similar in both treatment groups.

Overall, 139 of 152 participants (91.4%) took concomitant medications (Avonex group: 70 participants, 90.9%; BIIB017 group: 69 participants, 92.0%). The most common concomitant medications (taken by > 20% of participants overall) were paracetamol (84 participants [55.3%]), ibuprofen (52 participants [34.2%]), and methylprednisolone (37 participants [24.3%]).

Adverse Events

Overall, 129 of 152 participants (84.9%) experienced at least 1 TEAE during the study. TEAEs were reported in a similar percentage of participants in both treatment groups (Avonex group: 63 participants, 81.8%; BIIB017 group: 66 participants, 88.0%). The most common TEAEs (reported in > 10% of participants) by preferred term in decreasing frequency were MS relapse (48 participants [31.6%]), influenza-like illness (40 participants [26.3%]), headache (30 participants [19.7%]), injection site erythema (29 participants [19.1%]), and pyrexia (22 participants [14.5%]).

Of these, the largest between group difference was for injection site erythema: 4 participants (5.2%) in the Avonex group and 25 participants (33.3%) in the BIIB017 group; followed by MS relapse: 30 participants (39.0%) in the Avonex group and 18 participants (24.0%) in the BIIB017 group.

By PT, severe TEAEs experienced by ≥ 2 participants overall were MS relapse (7 participants [4.6%]), complicated appendicitis and suicidal ideation (2 participants [1.3%] each). The severe TEAE of MS relapse was reported for 5 participants (6.5%) in the Avonex group and 2 participants (2.7%) in the BIIB017 group. The severe TEAE of complicated appendicitis was reported for 2 participants (2.6%) in the Avonex group and 0 participants in the BIIB017 group. The severe TEAE of suicidal ideation was reported for 2 participants (2.6%) in the Avonex group and 0 participants in the BIIB017 group.

The percentage of participants who had TEAEs that were related to study treatment was similar in both the Avonex group (44 participants [57.1%]) and BIIB017 group (49 participants [65.3%]). The related TEAE experienced by ≥ 20% participants overall were influenza-like illness (Avonex group: 24 participants, 31.2%; BIIB017 group: 16 participants, 21.3%).

The Investigator considered the following treatment-emergent SAEs related to study treatment: abdominal pain, haematuria, and haemorrhagic ovarian cyst (all 3 events were part of the same case that occurred in a participant in the Avonex group.

Overall, 9 participants (5.9%) had TEAEs that led to discontinuation of study treatment (Avonex group: 6 participants, 7.8%; BIIB017 group: 3 participants, 4.0%). The most common TEAEs that led to discontinuation of study treatment in > 1 participant overall by PT were suicidal ideation and MS relapse (2 participants [1.3%] each). Suicidal ideation was reported for 2 participants (2.6%) in the Avonex group and 0 participants in the BIIB017 group. MS relapse was reported for 1 participant (1.3%) in each group. No deaths were reported.

Overall, the only TEAE by PT that led to withdrawal from the study in ≥ 2 participants was suicidal ideation (2 participants, 1.3%). The onset of these events was Day 262 and Day 504, respectively. The Investigator assessed the intensity of the events of suicidal ideation as severe and considered the events to be related to the study treatment for both participants. Depression and suicidal ideation are known to occur in increased frequency in the MS population and are labelled events for Avonex. Details of suicidal ideation are sufficiently listed in the Avonex European Union product information.

Clinical laboratory

Clinical laboratory assessments were consistent with the known safety profile of Avonex. As of the data cut-off date (Week 96), 21 participants had lymphocyte counts < 0.91 × 109cells/L, 10 participants in the Avonex group and 11 participants in the BIIB017 group. Twenty-four participants had lymphocyte counts < LLN, 11 participants in the Avonex group and 13 participants in the BIIB017 group. Decreased peripheral blood counts have been reported in patients receiving interferons.

Blood chemistry

There were no clinically meaningful trends in mean values for blood chemistry results. Mean ALT and AST concentrations were higher in the BIIB017 group than in the Avonex group. Abnormal alanine aminotransferase and aspartate aminotransferase values were found in the following categories, but none of the participants had laboratory results that met Hy's law criteria: ≥ 3 to < 5 × ULN; ≥ 5 to < 10 × ULN; ≥ 10 to < 20 × ULN. There were no clinically meaningful trends in other laboratory measurements.

Vital signs and electrocardiogram evaluations were also consistent with the known safety profile of Avonex.

Immunogenicity

Overall, 150 participants were included in the immunogenicity analysis (75 participants each in the Avonex and BIIB017 groups). A total of 58 participants (38.7%) tested positive for anti-IFN β-1a

antibodies (Avonex group: 28 participants, 37.3%; BIIB017 group: 30 participants, 40.0%) and 15 participants (10.0%) tested positive for neutralizing IFN β-1a antibodies (Avonex group: 13 participants, 17.3%; BIIB017: 2 participants, 2.7%). Incidence of anti-IFN β-1a antibodies was similar between Avonex and BIIB017, while the incidence of neutralizing IFN β-1a antibodies was lower in the BIIB017 group. Although there was no formal analysis done, no significant AEs related to immunogenicity were reported and there was no apparent impact on safety or clinical efficacy, although the analysis was limited by the low incidence of immunogenicity.

8.3. Discussion

Results from Study 105MS306 Part 1 demonstrated a similar safety profile to that observed in the adult population. Avonex was generally well tolerated; most participants experienced events that were of mild or moderate severity, and the number of participants in the Avonex group who experienced TEAEs leading to treatment discontinuation was low (<10%). The incidence and type of AEs observed was generally consistent with the known safety profile of Avonex. The haematologic findings and elevated liver function tests were consistent with those seen in previous trials of Avonex.

Safety data for Avonex in the paediatric population are currently described in the Avonex EU PI section 4.8. Since there are no new or significant safety findings from Study 105MS306, the data from this study have not been added to SmPC section 4.8.

9. PRAC advice

Not applicable.

10. Changes to the Product Information

As a result of this variation, section 5.1 (Pharmacodynamic properties) of the SmPC was updated and the following paragraphs included:

"In an open-label randomised active controlled trial, 152 participants were randomly assigned in a 1:1 ratio to treatment with peginterferon beta-1a, administered subcutaneously at a dose of 125 µg every 2 weeks, or Avonex, administered at a dose of 30 µg once weekly by intramuscular (IM) injection, for 96 weeks.

At Week 96, the adjusted ARR (95% CI) was 0.527 (0.340, 0.816) in the Avonex group and 0.285 (0.172, 0.471) in the peginterferon beta-1a group. The mean (SD) participant relapse rate was 0.82 (1.953) in the Avonex group and 0.34 (0.798) in the peginterferon beta-1a group."

Upon request, data from the primary analysis was reflected in the SmPC; complementing the description of the study to include the ARR at week 48:
"The primary endpoint, the adjusted ARR at week 48 (95% CI), was 0.521 (0.322, 0.843) in the Avonex group and 0.386 (0.231, 0.646) in the peginterferon beta-1a group. The mean (SD) participant relapse rate was 0.81 (1.994) in the Avonex group compared to 0.40 (0.907) in the peginterferon beta-1a group. At week 96…".