Amsterdam, 26 February 2026
EMADOC-1700519818-2771158
Human Medicines Division

Assessment report for paediatric studies submitted in accordance with Article 46 of regulation (EC) No 1901/2006, as amended

Plegridy

Peginterferon beta-1A

Procedure no: EMA/PAM/0000320082

Note

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

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1. Introduction

On 16 December 2025, the MAH submitted a final report for Part 1 of a paediatric study for Plegridy, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

This procedure concerns evaluation of the final analysis for part 1 (i.e., results through Week 96). The interim analysis for subjects that completed at least 48-weeks has been assessed previously (part 1a with data cut-off 24aug2024. See EMA/PAM/0000245467 and EMA/VR/0000286235). Only part 1a (the interim analysis) was part of the Plegridy PIP.

Part 2, the open-label extension period of the study (up to Week 192), is still ongoing.

The MAH has not submitted a critical expert review or a discussion on whether the submitted data have any regulatory consequences.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Study 105MS306 is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

The pharmaceutical formulation used in the study 105MS306 was Plegridy solution for injection, either in a prefilled autoinjector pen or prefilled syringe. In this assessment report, the product names Plegridy and BIIB017 are used interchangeably. No specific paediatric formulation is available or under development.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- **Study 105MS306 Part 1** (a+b)

An open-label, randomized, multicenter, active-controlled, parallel-group study to evaluate the safety, tolerability, and efficacy of BIIB017 in pediatric 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

Description

Open-label, randomized, multicenter, active-controlled, parallel-group study patients 10- <18 years with RRMS. This report provides the results for Part 1. In Part 2 (up to Week 192), the open-label extension period of the study, the long-term safety of BIIB017 in the pediatric RRMS population will be investigated and reported in the final CSR upon study completion.

After stratification in part 1, participants were randomized 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.

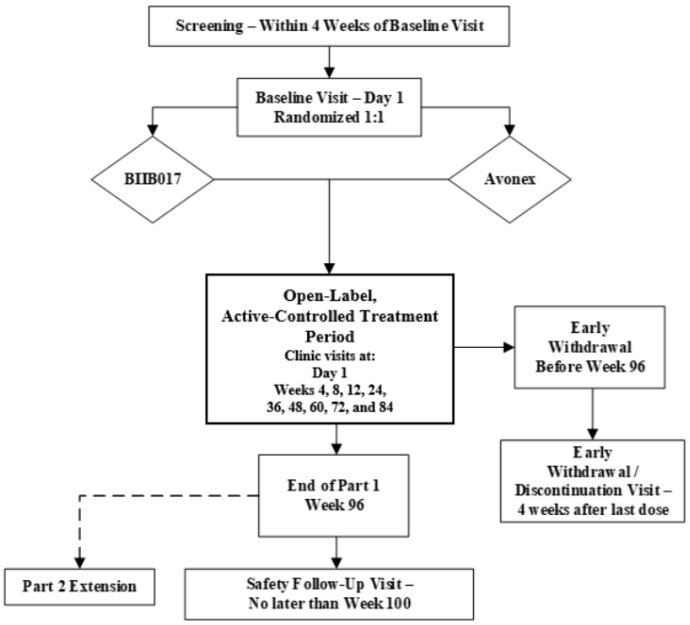


Figure 1. Study Design Schematic for the Randomized Phase - Part 1

Methods

Study participants

Key inclusion criteria were:

- Male and female patients, aged 10 - < 18 years
- Diagnosis of RRMS as defined by the revised consensus definition for pediatric MS [Krupp 2013; Polman 2011] and EDSS score between 0.0 and 5.5, inclusive, at the time of randomization (Day 1).
- ≥ 1 relapse in the 12 months prior to randomization (Day 1) or ≥ 2 relapses in the 24 months prior to randomization (Day 1) or have evidence of asymptomatic disease activity (Gd-enhancing lesions) on brain MRI in the 6 months prior to randomization (Day 1).

Key exclusion criteria were:

- Primary progressive, secondary progressive, or progressive relapsing MS. These conditions required the presence of continuous clinical disease worsening over a period of at least 3 months. Participants with these conditions may also have superimposed relapses but were distinguished from relapsing participants by the lack of clinically stable periods or clinical improvement.
- Occurrence of an MS relapse that occurred within 30 days prior to randomization (Day 1) and/or the participant had not stabilized from a previous relapse prior to randomization (Day 1).

Treatments

Test treatment: BIIB017/peginterferon beta-1a (Plegridy) at a maintenance dose of 125 µg SC every 2 weeks. To mitigate flu-like symptoms, patients were titrated as follows: 63 µg on Day 1, 94 µg at Week 2, and 125 µg at Week 4 and onwards

Active comparator: interferon beta-1a (Avonex), at a maintenance dose of 30 µg once weekly by IM injection according to local prescribing information. To reduce the incidence and ameliorate flu-like symptoms, patients were titrated as follows: was 7.5 µg and increased by 7.5 µg each week for 3 weeks until 30 µg was achieved. At the discretion of the treating neurologist, dose titration may not have been necessary.

Objective(s)

The primary and secondary objectives were to:

- evaluate the safety, tolerability, and descriptive efficacy of BIIB017 in pediatric participants with relapsing-remitting multiple sclerosis (RRMS)
- assess the pharmacokinetics (PK) of BIIB017 in pediatric participants with RRMS.

The exploratory Objective was to collect additional efficacy information.

Outcomes/endpoints

The primary endpoint of the study was: Annualized relapse rate (ARR) at Week 48.

Secondary efficacy endpoints were:

- 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

Exploratory endpoints were:

- Time to progression of disability at Weeks 48 and 96 as measured by ≥ 1.0-point increase on the EDSS from baseline EDSS ≥ 1.0 that was sustained for 12 weeks, or ≥ 1.5-point increase on the EDSS from baseline EDSS = 0 that was sustained for 12 weeks
- Number of new T1 hypointense lesions on brain MRI scans at Weeks 24, 48, and 96

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 considerations in setting the sample size were based on a projected dropout rate of approximately 30% over a 2-year period and approximately 142 participants at ≥ 60 sites globally, aged 10 to < 18

years, were planned to be randomized in Part 1 of the study to obtain a total of at least 100 evaluable participants who have completed at least 48 weeks of treatment, and to include the following:

- At least 12 evaluable participants for the primary endpoint in the 10 to < 13 years age group
- At least 80 evaluable participants for the primary endpoint in the 13 to < 18 years age group

Randomisation and blinding (masking)

Participants were stratified by age group (10 to < 13 years, 13 to < 15 years, or 15 to < 18 years), IFN use (yes/no) during the 4 weeks prior to study entry, and GA use (yes/no) during the 4 weeks prior to study entry. After stratification, participants were randomized using IXRS in a 1:1 ratio to treatment with BIIB017 or Avonex for Part 1 of this Study.

The study was open-label.

Statistical Methods

Analysis populations:

- 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.

Summary of statistical analysis plan for efficacy endpoints is presented in Table 1.

Table 1. Summary of statistical analysis plan - Part 1

Primary Efficacy Endpoints/ [Estimands]	**Statistical Method**	**Analysis Population**
ARR at Week 48	LS means ARR from a negative binomial generalized linear model for each of the study drug groups (Avonex and BIIB017). Note that for the purposes of ARR analyses, "years" are calendar years.	FAS and Per Protocol Set
Secondary Efficacy Endpoints/ [Estimands][a]	**Main Statistical Method**	**Analysis Population**
ARR at Week 96	LS means ARR from a negative binomial generalized linear model for each of the study drug groups (Avonex and BIIB017). Note that for the purposes of ARR analyses, "years" are calendar years.	FAS and Per Protocol Set
Number of new or newly enlarging T2 hyperintense lesions on brain MRI scans at Weeks 24, 48, and 96	LS mean number of new/newly enlarging T2 hyperintense lesions (relative to baseline images) from a negative binomial generalized linear model for each of the study drug groups (Avonex and BIIB017).	FAS
Proportion of participants free of new or newly enlarging T2 hyperintense lesions on brain MRI scans at Weeks 24, 48, and 96	Fraction of participants with 0 counts for each of the study drugs (Avonex and BIIB017). 95% distribution-free (Clopper-Pearson) CI.	FAS
Number of Gd-enhancing lesions on brain MRI scans at Weeks 24, 48, and 96	Summary statistics were presented for each of the study drug groups (Avonex and BIIB017).	FAS
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	Fraction of participants with 0 counts for both lesion types for each of the study drugs (Avonex and BIIB017). 95% distribution-free (Clopper-Pearson) CI.	FAS
Time to first relapse	For each treatment group, Kaplan-Meier (product-limit) nonparametric time-to-event estimates of the 25, 50, and 75 percentiles of the time to first relapse were provided based on the log-log transform.	FAS

Proportion of participants free of relapse up to Weeks 48 and 96	The proportion of participants assigned to each treatment who did not experience a relapse while on study medication during the period in question[b].	FAS
Change from baseline in the EDSS score at Weeks 48 and 96	Statistical summary of the scores and change from baseline for each study group.	FAS
Change from baseline in cognition as measured by the SDMT at Weeks 24, 48, 72, and 96	Statistical summary of the scores and change from baseline for each study group.	FAS
Change from baseline in the quality of life as measured by the PedsQL at Weeks 24, 48, 72, and 96	Statistical summary of the scores and change from baseline for each study group. Self-reports and parent scores were summarized separately. The actual scores were analyzed using analysis of covariance, adjusting for baseline PedsQL score and participant's age group.	FAS
Exploratory Efficacy Endpoints/ [Estimands][a]	**Main Statistical Method**	**Analysis Population**
Time to progression of disability at Week 48 and at Week 96 as measured by ≥ 1.0-point increase on the EDSS from baseline EDSS ≥ 1.0 that is sustained for 12 weeks, or ≥ 1.5-point increase on the EDSS from baseline EDSS = 0 that is sustained for 12 weeks	For each treatment group, Kaplan-Meier (product-limit) nonparametric time-to-event estimates of the 25, 50, and 75 percentiles of the time to disability progression were provided.	FAS
Number of new T1 hypointense lesions on brain MRI scans at Weeks 24, 48, and 96	LS means for new lesion count from a negative binomial generalized linear model for each of the study drug groups relative to baseline images (Avonex and BIIB017).	FAS
Secondary PK Endpoint	**Main Statistical Method**	**Analysis Population**
PK parameters, including exposure (AUC_{tau}), C_{max} at steady state, and T_{max} at steady state	The population PK analysis plan was included in Appendix 16.1.10.	PK Analysis Set
Secondary Safety Endpoints	**Main Statistical Method**	**Analysis Population**
Incidence of AEs, SAEs, and AEs leading to study treatment discontinuation.	Descriptive statistics and frequency tables were used to summarize safety data. No formal statistical testing was planned.	Safety Analysis Set
Change over time in growth parameters, including height, weight, and Tanner Score. Immunogenicity as assessed by the development of binding and neutralizing antibodies to IFN β-1a (all participants) and/or binding antibodies to PEG (BIIB017-treated participants). Change from baseline in depression as assessed by MINI-KID. Change from baseline in vital signs and 12-lead ECG parameters. Change over time in hematology, clinical laboratory values (including liver, renal, and thyroid function), and coagulation.	AEs will be coded using the MedDRA, using the latest available version (Version 27.0 or later). The antibody titers were analyzed by scheduled visit for each treatment group and overall, with the number and percent of participants with positive titers and quantifiable titers. MINI and MINI-KID scores were summarized statistically by domain for each visit scheduled. Vital signs and the change from baseline were summarized with summary statistics at Baseline and each scheduled visit for each of the treatment groups and overall. In addition, the number and percent of participants in each treatment group experiencing clinically relevant abnormalities at any visit were presented. 12-lead ECG test results were categorized then summarized by count and percent for each category in each treatment group at each scheduled visit. Shift tables were provided. Laboratory results were coded to grades according to hematology and qualitative urinalysis parameters. Shift tables were provided.	

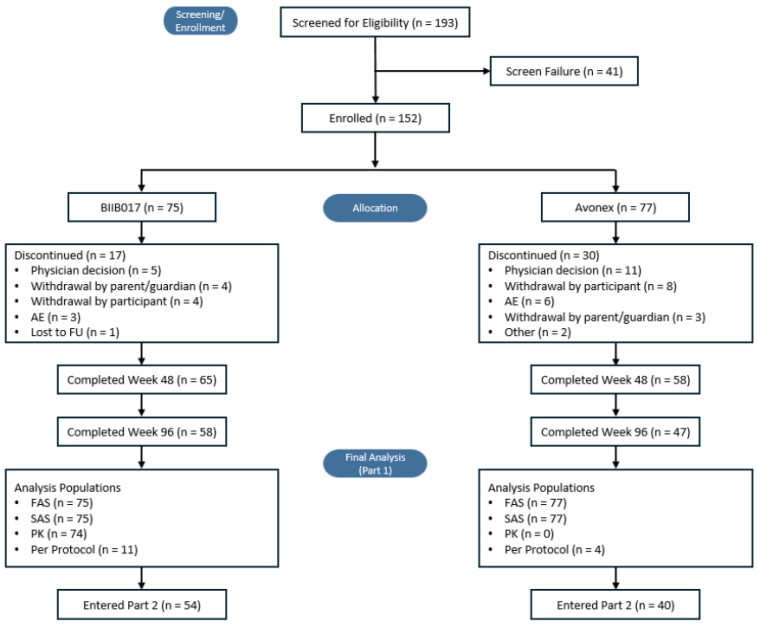
[a] See Section 8 for the full list of endpoints for Part 1.

[b] The proportion of participants relapsed and the proportion of participants who are free of relapse are complementary measures.

Source: CSR Table 6

Results

Participant flow



Source: Section 14.1.1, Output 1 and Output 2
n = number of participants

Figure 2. CONSORT Flow Diagram for Disposition of Participants in Part 1 (source: CSR Figure 2)

Recruitment

Part 1 through Week 96 was conducted at 51 sites in 20 countries. First patient was treated on 18 October 2019, and the data cutoff date for this final analysis of Part 1 was 18 June 2025.

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. As of the data cutoff date, 123 participants (80.9%) completed Week 48 of the study: 58 participants (75.3%) in the Avonex group and 65 participants (86.7%) in the BIIB017 group. There were 105 participants (69.1%) who completed Week 96 of the study: 47 participants (61.0%) in the Avonex group and 58 participants (77.3%) in the BIIB017 group.

As of the data cutoff date, 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. Overall, 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%]).

As of the data cutoff date, 47 participants (30.9%) were withdrawn from the study overall: 30 participants (39.0%) 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 (SD) age of the 152 participants enrolled in the Part 1 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 pre-study relapse was 6.2 (7.25) months. Most participants (137 of 152) had an EDSS score between 0 and 2 at Baseline.

Of 152 participants, 35 participants (23%) took MS medication prior to enrollment. The most common medication (taken by > 10% of participants overall) prior to enrollment was interferon β-1a, which was taken by 17 participants (11%). The percentage of participants who took prior MS medications was similar between participants in both groups.

Table 2. Summary of Major Protocol Deviations (Safety analysis set)

	Avonex (N=77)	BIIB017 (Plegridy) (N=75)	Total (N=152)
Number of subjects dosed	77 (100)	75 (100)	152 (100)
Number of subjects with at least one major deviation	72 (93.5)	64 (85.3)	136 (89.5)
LABORATORY ASSESSMENT CRITERIA	72 (93.5)	54 (72.0)	126 (82.9)
STUDY PROCEDURES CRITERIA	23 (29.9)	15 (20.0)	38 (25.0)
INFORMED CONSENT CRITERIA	17 (22.1)	16 (21.3)	33 (21.7)
VISIT SCHEDULE CRITERIA	5 (6.5)	10 (13.3)	15 (9.9)
INVESTIGATIONAL PRODUCT (IP) COMPLIANCE	8 (10.4)	3 (4.0)	11 (7.2)
ADMINISTRATIVE CRITERIA	5 (6.5)	2 (2.7)	7 (4.6)
ELIGIBILITY AND ENTRY CRITERIA	3 (3.9)	2 (2.7)	5 (3.3)
SERIOUS ADVERSE EVENT CRITERIA	2 (2.6)	3 (4.0)	5 (3.3)
CONCOMITANT MEDICATION CRITERIA	3 (3.9)	1 (1.3)	4 (2.6)
EFFICACY CRITERIA	4 (5.2)	0	4 (2.6)
OTHER: DELEGATION	2 (2.6)	1 (1.3)	3 (2.0)
OTHER: A SITE STAFF PERFORMING A NON-DELEGATED TASK	1 (1.3)	0	1 (0.7)
OTHER: OTHER	1 (1.3)	0	1 (0.7)
OTHER: STUDY PROCEDURES	1 (1.3)	0	1 (0.7)
Number of Subjects With At Least One Major Deviation Related To Covid-19 Pandemic Measures	1 (1.3)	3 (4.0)	4 (2.6)
INFORMED CONSENT CRITERIA	0	2 (2.7)	2 (1.3)
STUDY PROCEDURES CRITERIA	1 (1.3)	1 (1.3)	2 (1.3)
EFFICACY CRITERIA	1 (1.3)	0	1 (0.7)

NOTE 1: Number in parentheses are percentages.
NOTE 2: Subject ID XXX-XXX was a screen failure in XXXX. This subject was re-screened in XXXX and enrolled under the Subject ID XXX-XXX.
Source: CSR Table 10

Number analysed

The FAS population included all 152 all randomized participants who received at least 1 dose of study treatment in Part 1.

Efficacy results

Primary Endpoint	**Results**
ARR at Week 48	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.
Secondary Endpoints Related to Efficacy	**Results**
ARR at Week 96	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. The mean (SD) participant relapse rate was 0.82 (1.953) in the Avonex group and 0.34 (0.798) in the BIIB017 group.
Proportion of participants free of new or newly enlarging T2 hyperintense lesions on brain MRI scans at Weeks 24, 48, and 96	The number of participants free of new or newly enlarging T2 hyperintense lesions on brain MRI scans at Week 24 was 7 of 72 participants in the Avonex group (0.097; 95% CI: 0.040, 0.190) and 14 of 70 participants in the BIIB017 group (0.200; 95% CI: 0.114, 0.313); at Week 48 was 4 of 62 participants in the Avonex group (0.065; 95% CI: 0.018, 0.157) and 9 of 65 participants in the BIIB017 group (0.138; 95% CI: 0.065, 0.247); and at Week 96 was 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).
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	The number of participants free of new MRI activity at Week 24 was 7 of 72 participants in the Avonex group (0.097; 95% CI: 0.040, 0.190) and 14 of 70 participants in the BIIB017 group (0.200; 95% CI: 0.114, 0.313); at Week 48 was 4 of 62 participants in the Avonex group (0.065; 95% CI: 0.018, 0.157) and 9 of 65 participants in the BIIB017 group (0.138; 95% CI: 0.065, 0.247); and at Week 96 was 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).
Number of new or newly enlarging T2 hyperintense lesions on brain MRI scans at Weeks 24, 48, and 96	The adjusted mean (95% CI) cumulative number of new or newly enlarged T2 hyperintense lesions at Week 96 was 20.51 (95% CI: 14.07, 29.90) in the Avonex group and 18.19 (95% CI: 12.63, 26.19) in the BIIB017 group.
Number of Gd-enhancing lesions on brain MRI scans at Weeks 24, 48, and 96	The overall mean (SD) number of Gd-enhancing lesions at Week 24 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 was 0.9 (3.17): 1.3 (4.23) in the Avonex group and 0.5 (1.59) in the BIIB017 group; and at Week 96, was 0.5 (1.30): 0.6 (1.55) in the Avonex group and 0.4 (1.05) in the BIIB017 group.
Time to first relapse and proportion of participants free of relapse up to Weeks 48 and 96	The estimated Kaplan-Meier proportion of participants who were relapse free at Week 48 was 0.676 in the Avonex group and 0.764 in the BIIB017 group; at Week 72 was 0.627 in the Avonex group and 0.719 in the BIIB017 group; and at Week 96 was 0.530 in the Avonex group and 0.719 in the BIIB017 group.
Change from baseline in cognition as measured by the SDMT at Weeks 24, 48, 72, and 96	The mean (SD) change from baseline in SDMT score at Week 48 was 4.5 (8.75) in the Avonex group and 1.3 (8.51) in the BIIB017 group, and at Week 96 was 7.9 (11.64) in the Avonex group and 3.5 (9.67) in the BIIB017 group.
Change from baseline in the EDSS score at Weeks 48 and 96	The mean (SD) change from baseline in EDSS score at Week 48 was -0.1 (0.70) in the Avonex group and 0.1 (0.64) in the BIIB017

	group, and at Week 96 was 0.0 (0.74) in the Avonex group and 0.1 (0.67) in the BIIB017 group.
Change from baseline in the quality of life as measured by the PedsQL at Weeks 24, 48, 72, and 96	The mean scores in each dimension were similar between Avonex and BIIB017 treatment groups, except for the Work/School dimension where slight differences in the mean scores were observed between the treatment groups.
Exploratory Endpoints	**Results**
Time to progression of disability at Weeks 48 and 96 as measured by ≥ 1.0-point increase on the EDSS from baseline EDSS ≥ 1.0 that is sustained for 12 weeks, or ≥ 1.5-point increase on the EDSS from baseline EDSS = 0 that is sustained for 12 weeks	Progression of disability occurred in 7 participants (9.1%) in the Avonex group and 5 participants (6.7%) 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).
Number of new unenhancing T1 hypointense lesions on brain MRI scans at Weeks 24, 48, and 96	The adjusted mean 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. The adjusted mean number of new unenhancing T1 hypointense lesions at Week 24 relative to that in the 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 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; and at Week 96 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.

Source: CSR Table 11

Safety results

Deaths

There were no deaths reported during part 1 of the study.

AEs

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%). The most common TEAEs (reported in > 10% of participants) were multiple sclerosis 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%]).

Table 3. Overall summary of treatment-emergent adverse events (safety analysis set)

	Avonex (N=77)	BIIB017 (Plegridy) (N=75)	Total (N=152)
Number of subjects with any event (a)	63 (81.8)	66 (88.0)	129 (84.9)
Severity (b)			
Mild	17 (22.1)	23 (30.7)	40 (26.3)
Moderate	34 (44.2)	38 (50.7)	72 (47.4)
Severe	12 (15.6)	5 (6.7)	17 (11.2)
Related event (b, c)	44 (57.1)	49 (65.3)	93 (61.2)
Serious event	12 (15.6)	8 (10.7)	20 (13.2)
Related serious event	1 (1.3)	0	1 (0.7)
Events leading to drug discontinuation	6 (7.8)	3 (4.0)	9 (5.9)
Events leading to study withdrawal	5 (6.5)	4 (5.3)	9 (5.9)
Number of subjects who died	0	0	0

NOTE 1: Numbers in parentheses are percentages.
NOTE 2: A subject can appear in more than one category.
NOTE 3. AE occurring after subjects changed to alternative MS therapy are omitted.
(a) Subjects are counted if they have any event prior to withdrawal from study.
(b) Each subject counted once at maximum severity. Events occurring after change to alternate MS medication are excluded.
(c) Related as assessed by the investigator.

Source: CSR Section 14.3.2, Output 1

Severe TEAEs experienced by ≥ 2 participants overall were multiple sclerosis relapse (7 participants [4.6%]), complicated appendicitis and suicidal ideation (2 participants [1.3%] each). 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%]).

Other Safety Parameters – clinical laboratory results

Hematology Results: PCS hematology laboratory abnormalities at postbaseline included WBC count total in 14 participants: value < 3.0 × 109/L in 12 participants (8%) and value ≥ 16 × 109/L in 2 participants (1%); lymphocyte count in 13 participants: value < 0.5 × 109/L in 3 participants (2%) and value < 0.8 × 109/L in 13 participants (9%); neutrophil count in 29 participants: value ≤ 1.0 × 109/L in 6 participants (4%), value < 1.5 × 109/L in 26 participants (17%), and ≥ 12 × 109/L in 3 participants (2%); hemoglobin value ≤ 100 g/L in 3 participants (2%); and platelet count ≤ 100 × 109 in 1 participant.

As of the data cutoff date, 21 participants had lymphocyte counts < 0.91 × 109cells/L, 10 participants in the Avonex group and 11 participants in the BIIB017 group (Section 14.3.3, Output 23). Twenty-four participants had lymphocyte counts < LLN, 11 participants in the Avonex group and 13 participants in the BIIB017 group. No participant who completed Part 1 (without entering Part 2), temporarily withheld medication during Part 1, or permanently discontinued treatment had a lymphocyte count below the LLN immediately before or on the day of discontinuation. One participant in the Avonex group, however, had an absolute lymphocyte count of 0.63 × 109 cells/L, 7 days after stopping treatment (within the dosing interval). No further absolute lymphocyte count measurements were available for this participant, so the recovery period could not be determined.

Table 4. Hematology shift from baseline (safety analysis set)

	Avonex (N=77)	BIIB017 (Plegridy) (N=75)	Total (N=152)
Shift to low (a)			
Basophils (10^9/L)	0/74	0/74	0/148
Basophils/Leukocytes (%)	0/74	0/74	0/148
Eosinophils (10^9/L)	0/74	0/74	0/148
Eosinophils/Leukocytes (%)	8/74 (10.8)	5/74 (6.8)	13/148 (8.8)
Hematocrit (L/L)	8/73 (11.0)	19/70 (27.1)	27/143 (18.9)
Hemoglobin (g/L)	10/75 (13.3)	13/67 (19.4)	23/142 (16.2)
Lymphocytes (10^9/L)	16/72 (22.2)	18/70 (25.7)	34/142 (23.9)
Lymphocytes/Leukocytes (%)	26/74 (35.1)	14/69 (20.3)	40/143 (28.0)
Monocytes (10^9/L)	9/68 (13.2)	15/72 (20.8)	24/140 (17.1)
Monocytes/Leukocytes (%)	15/65 (23.1)	18/70 (25.7)	33/135 (24.4)
Neutrophils (10^9/L)	21/71 (29.6)	44/74 (59.5)	65/145 (44.8)
Neutrophils/Leukocytes (%)	18/70 (25.7)	27/74 (36.5)	45/144 (31.3)
Platelets (10^9/L)	3/74 (4.1)	3/74 (4.1)	6/148 (4.1)
Erythrocytes (10^12/L)	3/76 (3.9)	3/72 (4.2)	6/148 (4.1)
Leukocytes (10^9/L)	17/73 (23.3)	47/71 (66.2)	64/144 (44.4)
Shift to high (b)			
Basophils (10^9/L)	20/69 (29.0)	11/67 (16.4)	31/136 (22.8)
Basophils/Leukocytes (%)	21/60 (35.0)	18/58 (31.0)	39/118 (33.1)
Eosinophils (10^9/L)	9/70 (12.9)	4/66 (6.1)	13/136 (9.6)
Eosinophils/Leukocytes (%)	14/62 (22.6)	16/61 (26.2)	30/123 (24.4)
Hematocrit (L/L)	2/74 (2.7)	4/74 (5.4)	6/148 (4.1)
Hemoglobin (g/L)	1/76 (1.3)	4/74 (5.4)	5/150 (3.3)
Lymphocytes (10^9/L)	13/73 (17.8)	4/74 (5.4)	17/147 (11.6)
Lymphocytes/Leukocytes (%)	19/73 (26.0)	30/74 (40.5)	49/147 (33.3)
Monocytes (10^9/L)	17/72 (23.6)	10/73 (13.7)	27/145 (18.6)
Monocytes/Leukocytes (%)	26/71 (36.6)	22/70 (31.4)	48/141 (34.0)
Neutrophils (10^9/L)	16/73 (21.9)	10/73 (13.7)	26/146 (17.8)
Neutrophils/Leukocytes (%)	23/73 (31.5)	18/69 (26.1)	41/142 (28.9)
Platelets (10^9/L)	3/72 (4.2)	1/74 (1.4)	4/146 (2.7)
Erythrocytes (10^12/L)	3/75 (4.0)	3/73 (4.1)	6/148 (4.1)
Leukocytes (10^9/L)	16/72 (22.2)	9/74 (12.2)	25/146 (17.1)

NOTE 1: Entries are number of post-baseline shifts/number at risk (percentage).
Number at risk for shift to low (or high) is the number of subjects whose baseline value was not low (or high) and who had at least one post-baseline value.
NOTE 2: Data collected after a change to alternative MS therapy are not included here.
(a) Shift to L (lowest post baseline value) includes normal to low, high to low, and unknown to low.
(b) Shift to H (highest post baseline value) includes normal to high, low to high, and unknown to high.

Source: CSR Section 14.3.3, Output 22

Blood Chemistry Results: Mean ALT and AST concentrations were higher in the BIIB017 group than in the Avonex group beginning in Week 24. Mean GGT concentrations were higher in the BIIB017 group than in the Avonex group beginning in Week 12, except for Week 36.

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 beginning in Week 24. Mean GGT concentrations were higher in the BIIB017 group than in the Avonex group beginning in Week 12, except for Week 36. 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. None of the participants had laboratory results that met Hy's law criteria.

Table 5. Shifts from baseline to maximum post-baseline; selected parameter: alanine aminotransferase (safety analysis set)

	Maximum post-baseline value						
Baseline	**Value <= 1 x ULN**	**1 x ULN < Value < 3 x ULN**	**3 x ULN <= Value < 5 x ULN**	**<=5 x ULN <= Value < 10 x ULN**	**<=10 x ULN <= Value < 20 x ULN**	**20 x ULN <= Value**	**Unknown**
Avonex (N=77)							
Value <= 1 x ULN	48 (62)	19 (25)	3 (4)	0	0	0	0
1 x ULN < Value < 3 x ULN	0	5 (6)	0	0	1 (1)	0	0
3 x ULN <= Value < 5 x ULN	0	0	0	0	0	0	0
5 x ULN <= Value < 10 x ULN	0	0	0	0	0	0	0
10 x ULN <= Value < 20 x ULN	0	0	0	0	0	0	0
20 x ULN <= Value	0	0	0	0	0	0	0
Unknown	0	0	0	0	0	0	0
BIIB017 (Plegridy) (N=75)							
Value <= 1 x ULN	41 (55)	24 (32)	3 (4)	0	1 (1)	0	0
1 x ULN < Value < 3 x ULN	0	4 (5)	0	1 (1)	0	0	0
3 x ULN <= Value < 5 x ULN	0	0	0	0	0	0	0
5 x ULN <= Value < 10 x ULN	0	0	0	0	0	0	0
10 x ULN <= Value < 20 x ULN	0	0	0	0	0	0	0
20 x ULN <= Value	0	0	0	0	0	0	0
Unknown	0	0	0	0	0	0	0

NOTE 1: Number of Subjects is based on subjects dosed with either baseline or post-baseline value in ITT population. This is the denominator for percentages in parentheses.
NOTE 2: Data collected after a change to alternative MS therapy are not included here.

Source: CSR Section 14.3.3, Output 10

Thyroid Stimulating Hormone Results: 1 participant in Avonex group had an AE of blood thyroid stimulating hormone decreased and 1 participant in BIIB017 group had an AE of blood thyroid stimulating hormone increased.

Coagulation: There were no trends in changes from baseline in any coagulation values in either group.

Endocrine test results: None of the reported abnormal endocrine test results were associated with AEs and were not clinically significant.

Urinalysis: There were no trends in changes from baseline in any urinalysis values in either group.

Vital Sign Measurements, ECG Findings, and Other Observations Related to Safety
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 18 of 151 participants (11.9%). Except for low pulse rate (12 of 77 participants [15.6%] in the Avonex group and 6 of 74 participants [8.1%] 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 in vital signs were generally similar in both treatment groups. There were no AEs associated with abnormal ECG shifts.

Immunogenicity assessments
Fifty-eight of 150 participants (38.7%) tested positive for anti-IFN β-1a antibodies (28 participants [37.3%] in the Avonex group and 30 participants [40.0%] in the BIIB017 group) and 15 participants (10.0%) 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).

2.3.3. Discussion on clinical aspects

This concerns the assessment of the final results of part 1 of the open-label pediatric study 105MS306.

Results of subjects that completed at least 48 weeks have been assessed previously (interim analysis; part 1; see EMA/PAM/0000245467 and EMA/VR/0000286235) which included the primary endpoint analysis (ARR at Week 48). Compared to that assessment, new data are from nine additional patients

that completed Week 96 (n=6 in Plegridy group; n=3 in Avonex group). I.e., only little new data were available for the final analysis.

Refer to the previous reports (EMA/PAM/0000245467 and EMA/VR/0000286235) for assessment of the study design, interim analysis results including pediatric-adult data comparison, and overall conclusion that the B/R for Plegridy remained positive. All PK-related data were available at the interim analysis and so also assessed previously (EMA/VR/0000286235). Part 2, the open-label extension, is still ongoing. The Part 2 CSR is expected to be shared in due course.

There were major protocol deviations in almost all patients in both treatment arms (n=136/89.5%), with 'laboratory assessment criteria' by far the most common (Plegridy n=54/72%; Avonex: n=72/93.5%). Those deviations align with the many out-of-normal-range blood laboratory results that are linked to the known safety profile of interferon-β-1a products. The out-of-range laboratory results also limitedly led to dose modification (in TEAE SOC 'investigations' and 'blood and lymphatic disorders' Plegridy n=4; Avonex: n=1), to discontinuation (TEAE SOC 'investigations', n=1 in each group), or to withdrawal (TEAE SOC 'investigations': Plegridy n=1; Avonex n=0). Therefore these protocol deviations do not alter safety conclusions for Plegridy. Treatment differences between Plegridy and Avonex on ARR at Week 48 were comparable in the FAS and PP analysis populations, which supports validity of the efficacy conclusions despite the many protocol deviations.

The final analysis results are generally consistent with that of the interim analysis, and with what has been reported for Plegridy in adults.

- Regarding efficacy, at Week 96, in line with Week 48 a lower ARR (95% CI) in the Plegridy (0.285; 0.172-0.471) vs. Avonex (0.527; 0.340-0.816) group was observed. The MRI-endpoint results also remained comparable with slightly more patients with free of new or newly enlarging T2 hyperintense lesions on MRI (Plegridy n=9 of 56 vs Avonex n=2 of 49). Mean changes in EDSS scores (±SD) at Weak 96 remained minimal (Plegridy: +0.1±0.67; Avonex: 0.0±0.74). The MAH should still update SmPC section 5.1 to reflect these most recent results as it is now limited to Week 48 data.
- Regarding safety, most common TEAEs reported in the Plegridy group were injection site erythema, influenza like illness, headache, pyrexia and Alanine aminotransferase increased. The most notable between-group differences in TEAE incidence were injection site erythema (Plegridy n=25/33.3% vs. Avonex n=4/5.2% - plausibly due to the SC vs IM route of administration), and multiple sclerosis relapse (Plegridy n=18/24% vs Avonex n=30/39%). There were no new findings regarding serious TEAEs and no additional patients in either group tested positive for neutralizing IFN-β-1a antibodies. Other safety results were also consistent with those assessed in EMA/PAM/0000245467 and EMA/VR/0000286235.

However, the SmPC text in section 4.8 on safety in paediatric patients is no longer supported. The text of ADRs may be incorrectly interpreted in that the ADR 'Alanine aminotransferase increased' is not a very common ADR in pediatric patients, although reported in n=9/12% in the Plegridy group at Week 96. An update of the SmPC is therefore requested.

The MAH has not proposed any regulatory actions at this time, which is not supported. In line with the conclusions of EMA/VR/0000286235 and because the final results of part 1 could potentially (indirectly) support extrapolation of adult data to children, the MAH is recommended to submit an extension of the indication for paediatric patients with RRMS based on paediatric extrapolation per ICH11A.

3. CHMP's overall conclusion and recommendation

This concerned the assessment of the final results of part 1 of the open-label pediatric study 105MS306. The MAH has not submitted a critical expert review or a discussion on if the submitted data have regulatory consequences.

Results of this final analysis were consistent with what has been assessed during review of the interim analysis (EMA/PAM/0000245467) and following type II variation procedure (EMA/VR/0000286235). Briefly, the annual relapse rate remained lower in the Plegridy group compared to the Avonex group, and Plegridy-related serious adverse events apart from multiple sclerosis relapse remained rare.

The MAH is recommended to submit an extension of the indication for paediatric patients with RRMS based on paediatric extrapolation (per ICH11A), in line with the conclusions of EMA/VR/0000286235 and because the final results of part 1 may (indirectly) support comparable efficacy to adults.

Moreover, currently only data up to Week 48 are included in the SmPC. The MAH is requested to update the SmPC with Week 96 results.

☒ **Fulfilled:**

In view of the available data regarding 105MS306 part 1 the MAH should either submit a variation in accordance with Articles 16 and 17 of Regulation (EC) No 726/2004 or provide a justification for not doing so. This should be provided without any delay and ***no later than 60 days after the receipt*** of these conclusions.

Specifically, and in line with the outcome of procedure EMA/VR/0000286235, the MAH is recommended to submit an extension of the indication for paediatric patients with RRMS based on paediatric extrapolation (as outlined in ICH11A) and in that variation also update the product information with final results of 105MS306 part 1. Otherwise, the MAH should start a dedicated variation procedure to update the product information as follows:

a. in section 4.8: reflect the final results by updating the following sentence as requested *[…]: **~~66~~ 58** patients in the peginterferon beta-1a group completed **~~48~~ 96** weeks of this study. The following adverse events which are very common in the adult population were also reported as very common in the paediatric population: injection site erythema, influenza like illness, headache and pyrexia.* ***The adverse event Alanine aminotransferase increased was very commonly reported (in adults commonly reported).***

b. in section 5.1: update text of 105MS306 to reflect results up to Week 96:

   i. replace results on completers at Week 48 by related results at Week 96

   ii. keep primary endpoint results, but add ARR at Week 96

   iii. replace results on number of participants free of new or newly enlarging T2 hyperintense lesions at Week 48 by related results at Week 96.

4. Request for supplementary information

Not Applicable