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Human Medicines Division

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

Plegridy

Peginterferon beta-1A

Procedure no: EMA/PAM/0000245467

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 Plegridy, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

The submitted study is part of the agreed paediatric investigation plan for peginterferon beta-1a (EMEA-001129-PIP01-M06).

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

CHMP comment

The MAH has submitted an interim report of study 105MS306. Phase 1a of the study (up to week 48) is completed, while Phase 1b (up to week 96) and the long-term extension (Phase 2) are 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 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 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 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

This was an open-label, randomized, multicenter, active-controlled, parallel-group study of BIIB017 in pediatric participants aged 10 to < 18 years for the treatment of RRMS. This report provides the results for Part 1 up to the data cut-off date (28 August 2024). 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, 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.

Methods

Study participants

This study enrolled male and female participants, aged from 10 to < 18 years old, with RRMS and an EDSS score between 0.0 and 5.5, inclusive, at the time of randomization (Day 1).

In addition, the patients 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 (MRI) in the 6 months prior to randomization (Day 1).

The main 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.
- History of severe allergic or anaphylactic reactions or known drug hypersensitivity.
- Known allergy to any component of Avonex or BIIB017 formulation.
- 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

Treatment:

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.

Comparator:

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. Note: At the discretion of the treating neurologist, dose titration may not have been necessary. Following titration, Avonex was administered once weekly by IM injection according to local prescribing information.

Objectives

The primary 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 the 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.

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 through week 48

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**
Number of new or newly enlarging T2 hyperintense lesions on brain MRI scans at Weeks 24 and 48	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 and 48	Fraction of participants with 0 counts for each of the study drugs (Avonex and BIIB017). 95% distribution-free (Clopper-Pearson) confidence interval.	FAS
Number of Gd-enhancing lesions on brain MRI scans at Weeks 24 and 48	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 and 48	Fraction of participants with 0 counts for both lesion types for each of the study drugs (Avonex and BIIB017). 95% distribution-free (Clopper-Pearson) confidence interval.	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 transform.	FAS
Proportion of participants free of relapse up to Week 48	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	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 and 48	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 and 48	Statistical summary of the scores and change from baseline for each study group. Self-reports and parent scores were summarized separately. The actual scores will be 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 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 was 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 and 48	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

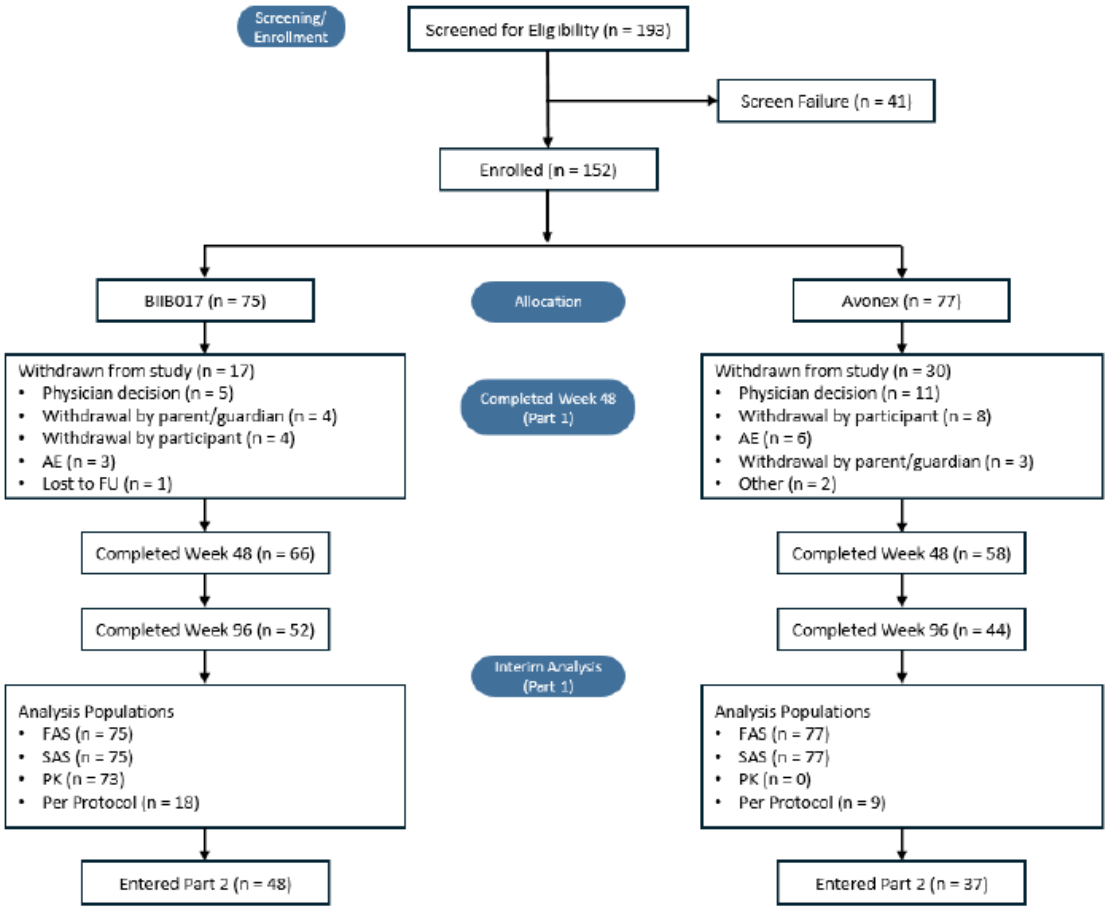
a See Section 8 of the CSR for the full list of endpoints for Part 1.
b The proportion of participants relapsed and the proportion of participants who are free of relapse are complementary measures.

Results

Participant flow

Participant flow up to data cut-off is presented in Figure 1.

Figure 1. Disposition of participants in part 1 up to data cut-off



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. As of the data cut-off date, 124 participants (81.6%) 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.

As of the data cut-off 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 (18 participants [11.8%]), 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 (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 (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.

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 efficacy endpoint ARR at Week 48

In the FAS overall, 111 participants (73%) did not relapse up to Week 48: 53 participants (69%) in the Avonex group and 58 participants (77%) in the BIIB017 group. A total of 59 relapses were reported: 35 in the Avonex group and 24 in the BIIB017 group. 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 estimated Kaplan-Meier proportion of participants who were relapse-free at Week 48 was 0.712 overall, 0.662 in the Avonex group, and 0.764 in the BIIB017 group.

Secondary efficacy endpoints

A total of 100 participants (66%) did not relapse up to Week 96: 45 participants (58%) in the Avonex group and 55 participants (73%) in the BIIB017 group. A total of 87 relapses were reported: 56 in the Avonex group and 31 in the BIIB017 group. 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 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.

Other secondary and exploratory endpoint results are presented in Table 2.

Table 2. Results of secondary and exploratory efficacy endpoints in study 105MS306 up to data cut-off

Endpoint	Avonex (n=77)[a]	BIIB017 (n=75)[a]
Participants free of new or newly enlarging T2 hyperintense lesions, n (relative to baseline, 95%CI)[b]		
Week 24	7 (0.097; 0.040, 0.190)	14 (0.200; 0.114, 0.313)
Week 48	4 (0.065; 0.018, 0.157)	9 (0.136; 0.064, 0.243)
Participants free of new MRI activity in the brain, n (relative to baseline, 95%CI)[b]		
Week 24	7 (0.097; 0.040, 0.190)	14 (0.197; 0.112, 0.309)
Week 48	4 (0.065; 0.018, 0.157)	9 (0.138; 0.065,0.247)
Number of new or newly enlarging T2 hyperintense lesions, adjusted mean (95%CI)[c]		
Week 24	11.59 (8.40, 15.99)	11.86 (8.55, 16.45)
Week 48	15.25 (10.79, 21.55)	17.76 (12.86, 24.53)
Week 96	22.65 (15.52, 33.04)	24.28 (16.56, 35.80)
Number of Gd-enhancing lesions, mean (SD)		
Week 24	1.7 (6.42)	1.1 (2.25)
Week 48	1.3 (4.23)	0.5 (1.59)
Week 96	0.6 (1.58)	0.5 (1.14)
Number of new T1 hypointense lesions, adjusted mean (95%CI)[d]		
Week 24	1.71 (1.05, 2.79)	2.42 (1.50, 3.90)
Week 48	1.05 (0.58, 1.91)	1.58 (0.89, 2.79)
Week 96	1.12 (0.52, 2.40)	1.38 (0.65, 2.96)
Change from baseline in SDMT, mean (SD)		
Week 48	4.6 (8.45)	1.2 (8.51)
Week 96	7.6 (11.48)	4.1 (9.31)
Change from baseline in EDSS score , mean (SD)		
Week 48	0.0 (0.962)	0.15 (0.769)
Week 96	-0.10 (0.682)	0.03 (0.695)
Progression of disability	n=6 (8%)	n=4 (5%)
Hazard ratio (95% CI)[e]		0.544 (0.152, 1.948)

a N at baseline
b Clopper-Pearson exact 95% confidence interval
c Estimated from a negative binomial regression model, adjusted for age group, use of either interferon beta 1-a or glatiramer acetate in the four weeks preceding enrollment, and baseline number of T2 hyperintense lesions.
d Estimated from a negative binomial regression model, adjusted for age group and baseline volume of T1 lesions.
e based on Cox proportional hazards model, adjusted for baseline EDSS score and age
SDMT= Symbol Digit Modality Test, EDSS= Expanded Disability Status Scale

Safety results

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 are described, including all available data collected for the remainder of Part 1 (through Week 96).

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.

As of the data cut-off date, 124 participants (81.6%) 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.

Adverse events

Overall summary of adverse events is presented in Table 3.

Table 3. Summary of adverse events up to data cut-off

	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	15 (19.5)	21 (28.0)	36 (23.7)
Moderate	33 (42.9)	38 (50.7)	71 (46.7)
Severe	12 (15.6)	5 (6.7)	17 (11.2)
Related event (b, c)	45 (58.4)	49 (65.3)	94 (61.8)
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 withdrawal	7 (9.1)	3 (4.0)	10 (6.6)
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.

Overall, the most common TEAEs (reported in > 20% of participants) by SOC were General disorders and administration site conditions (83 participants [54.6%]), Nervous system disorders (80 participants [52.6%]), and Infections and infestations (56 participants [36.8%]). The percentages of participants with TEAEs in each SOC was generally similar between Avonex and BIIB017 groups.

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 58.4% in the Avonex group (45 participants) and 65.3% in the BIIB017 group (49 participants).

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

Overall, 20 participants (13.2%) had at least 1 SAE during Part 1 of the study: 12 participants (15.6%) in the Avonex group and 8 participants (10.7%) in the BIIB017 group. Most common SOC were Nervous system disorders, Infections and infestations and Gastrointestinal disorders. SAEs in the Nervous system disorders SOC were reported for 11 participants (14.3%) in the Avonex group and 4 participants (5.3%) in the BIIB017 group. SAEs in the Infections and infestations SOC were reported for 2 participants (2.6%) in the Avonex group and 2 participants (2.7%) in the BIIB017 group. SAEs in the Gastrointestinal disorders SOC were reported for 1 participant (1.3%) in the Avonex group and 1 participant (1.3%) in the BIIB017 group.

By PT, treatment-emergent SAEs experienced by ≥ 2 participants overall were multiple sclerosis relapse and complicated appendicitis. 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%]).

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

Discontinuation due to adverse events

Overall, 10 participants (6.6%) had a TEAE that led to discontinuation of study treatment: 7 participants (9.1%) in the Avonex group and 3 participants (4.0%) in the BIIB017 group.

By PT, the 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. 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.

Clinical laboratory results

Shifts is various clinical laboratory parameters are presented in Table 4.

Table 4. Shifts in clinical laboratory parameters

	Avonex	BIIB017
Hematology		
Shift from baseline normal, high, or unknown values to low values (in ≥ 25.0% of participants)		
Leucosyte count	20.5%	60.6%
Neutrophil count	22.5%	58.1%
neutrophils/leukocytes	20.0%	35.1%
hematocrit	9.6%	25.7%
Shift from baseline normal, low, or unknown values to high values (in ≥ 25.0% of participants)		
Lymphocytes/leucosytes	24.7%	37.8%
Basophils/leucosytes	36.1%	29.3%
Basophil count	30.0%	16.4%
Monocytes/lucosytes	29.6%	28.6%
Eosinophils/leucosytes	21.0%	26.2%
Blood chemistry		
Shift from baseline normal, high, or unknown values to low values (in ≥ 25.0% of participants)	-	-

Shift from baseline normal, low, or unknown values to high values (in ≥ 25.0% of participants)		
Phosphate	32.4%	35.8%
ALT	28.6%	39.1%
Glucose	38.6%	21.1%
AST	14.9%	29.7%
Thyroid Stimulating Hormone		
Shift from baseline normal, high, or unknown values to low values (in ≥ 25.0% of participants)	15.3%	7.2%
Shift from baseline normal, low, or unknown values to high values (in ≥ 25.0% of participants)	18.3%	10.3%
Urinalysis		
Shift from baseline normal, high, or unknown values to low values (in ≥ 25.0% of participants)	-	-
Shift from baseline normal, low, or unknown values to high values (in ≥ 25.0% of participants)		
Protein	55.0%	63.3%
Occult blood	43.9%	35.9%
ketones	32.9%	40.3%

Shift tables are based on the concept of subjects being at-risk for a change in status from baseline. The denominator for each parameter and study arm combination is the number of subjects at-risk for the shift. The numerator is the number of at-risk subjects who experienced the shift in question. The rate is the percentage of at-risk subjects who experienced the shift in question.

As of the data cut-off date, 8 participants had lymphocyte counts < 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.

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.

Vital signs

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.

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

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.

Pharmacokinetics

Sparse sampling and PK modeling and simulation was used to determine the PK of BIIB017. Samples for PK analysis were drawn postdose on Day 1, postdose during Week 4 (including Days 1, 3, and 6), and postdose during Week 24. The following parameters were calculated: AUC_{tau}, C_{max} at steady state and Tmax at steady state.

The PK analysis dataset included 306 measurable PK observations from 75 subjects from Study 105MS306. Existing PPK model developed with data from adult subjects underpredicted the observed BIIB017 plasma concentration in pediatrics from Study 105MS306. The model was refined and thereafter used in simulations to generate steady-state C_{max}, C_{trough}, and $AUC_{0\text{-}tau}$ of adult and pediatric subjects included in the combined PK analysis dataset. Steady-state $AUC_{0\text{-}tau}$ in pediatric subjects is about 2.5 times greater than that of the adult subjects $AUC_{0\text{-}tau}$. This was consistent with the estimated lower apparent clearance in pediatric participants. Similarly, simulated steady-state C_{max} and C_{trough} were higher in pediatric compared to adult MS participants.

2.3.3. Discussion on clinical aspects

The MAH submitted an interim report of ongoing open-label study 105MS306 in paediatric patients 10 to ≤ 18 years of age with RRMS. In this study, peginterferon beta-1a (Plegridy) or interferon beta-1a (Avonex) are administered to patients for a total duration of 192 weeks. The interim report covers the study period through week 48 (Part 1a) which is completed, and the available data up to week 96 (Part 1b) up to the data cut-off on 24 August 2024. This study is part of the agreed paediatric investigation plan for peginterferon beta-1a (EMEA-001129-PIP01-M06).

The study design in general follows a conventional study in RRMS in terms of duration and endpoints. A total of 152 participants were enrolled and randomized in Part 1 of the study, of whom 124 completed week 48 of the study. As per data cut-off, 96 patients have completed week 96.

The primary efficacy outcome was adjusted ARR at week 48, which was lower in the Plegridy group (0.386, 95% CI 0.231, 0.646)) as compared to the Avonex group (0.521, 95% CI 0.322, 0.843). MRI endpoints were overall similar between Plegridy and Avonex, with slightly higher proportion of participants free of new or newly enlarging T2 hyperintense lesions or MRI activity in the Plegridy group as compared to Avonex on week 48. Changes in EDSS scores were minimal.

Most adverse events occurred in similar rate in both treatment groups. Treatment-related adverse events with largest between-group difference were injection site erythema, which occurred more commonly in the Plegridy group as compared to Avonex (33.3% vs. 7.8%). This may be due to different route of administration of the products (SC vs. IM). Overall, the most common treatment-emergent adverse events reported for Plegridy in the paediatric population are in line with those reported in adults.

Serious adverse events occurred in 13.2% of subjects, and apart from multiple sclerosis relapse occurred only in ≤2 patients per PT.

The known effects of Plegridy on hematology and blood chemistry in adults were observed also in the current study in children. A total of 2.7% of patients in the Plegridy group tested positive for neutralizing IFN-β-1a antibodies without apparent impact on efficacy or safety.

The MAH has not submitted a clinical overview to discuss the observed efficacy and safety profile of Plegridy in paediatric patients based on data available so far, the possible impact to the B/R of Plegridy or proposed any regulatory actions.

3. CHMP's overall conclusion and recommendation

The MAH submitted an interim report of ongoing open-label study 105MS306 in paediatric patients 10 to ≤ 18 years of age with RRMS. In this study, peginterferon beta-1a (Plegridy) or interferon beta-1a (Avonex) are administered to patients for a total duration of 192 weeks. The interim report covers the study period through week 48 (Part 1a) which is currently completed, and the available data up to week 96 (Part 1b) up to the data cut-off on 24 August 2024.

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

In terms of efficacy, the primary endpoint ARR at week 48 was lower in the Plegridy group as compared to Avonex. MRI efficacy results were in general similar in both Plegridy and Avonex groups.

Treatment-related adverse events in paediatric patients in general seem to be in line with those reported in adults. Serious adverse events apart from multiple sclerosis relapse were rare.

Considering that there is no paediatric information included in the SmPC at the moment and that the interim report completes the requirement of the PIP and provides efficacy and safety data for a period of ~1 year of treatment, including the primary endpoint at week 48, the MAH was requested to provide a critical review of paediatric data available so far, the observed efficacy and safety profile (including comparisons to adult data in particular in terms of safety) and to justify why an SmPC variation is not required at this point (e.g. to include data in SmPC section 5.1). The MAH declared that they intend to submit a labelling update, including a critical review of the observed efficacy and safety profile, as requested, in a separate Type II variation. This is acceptable, provided that this variation is submitted within 60 days after adoption of the CHMP conclusion.

☒ **Fulfilled**: In view of the available data regarding efficacy and safety data in paediatric population, the MAH should submit a variation in accordance with Articles 16 and 17 of Regulation (EC) No 726/2004. The MAH has agreed on this. This should be provided without any delay and *no later than 60 days after the receipt* of these conclusions.

4. Request for supplementary information

Based on the data submitted, the MAH should address the following questions as part of this procedure:

1. Considering that there is no paediatric information included in the SmPC at the moment and that the interim report completes the requirement of the PIP and provides efficacy and safety data for a period of ~1 year of treatment, including the primary endpoint at week 48, the MAH is requested to provide a critical review of paediatric data available so far, the observed efficacy and safety profile (including comparisons to adult data in particular in terms of safety) and to justify why an SmPC variation is not required at this point (e.g. to include data in SmPC section 5.1).

The timetable is a 30-day response timetable with clockstop.

MAH responses to Request for supplementary information

The MAH acknowledges rapporteur's comment and intends to submit the labelling updates based on the data from CHARGE study in a separate Type II variation in quarter 3 (Q3) of 2025. The currently submitted interim CSR for the CHARGE study (105MS306) provides a review of the available paediatric data, including descriptive efficacy in section 11, and safety in section 12. A critical review of the observed efficacy and safety profile (including comparisons to adult data in particular in terms of safety) will be provided in the planned Type II submission in support of the label update.

Assessment of the MAH's response

The MAH was requested to provide a critical review of paediatric data available so far, and justify why an SmPC variation is not required at this point.

The MAH declared that they intend to submit a labelling update in a separate Type II variation in Q3 2025; and that a critical review of the observed efficacy and safety profile (including comparisons to adult data, in particular in terms of safety) will be provided within this variation procedure.

This approach is accepted, provided that the variation is submitted within 60 days after adoption of the CHMP conclusion.