EMADOC-1700519818-2324069
11 December 2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Plegridy

International non-proprietary name: Peginterferon beta-1A

Procedure No. EMA/VR/0000286235

Note

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

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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 11 July 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 sections 4.2, 4.8, 5.1 and 5.2 of the SmPC based on interim results from study 105MS306. This is 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.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0419/2023 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMEA-001129-PIP01-11-M06 was completed.

The PDCO issued an opinion on compliance for the PIP EMA/PE/0000273951.

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

The current variation concerns an update of sections 4.2, 4.8, 5.1 and 5.2 of the Plegridy (peginterferon beta-1a, BIIB017) based on interim results from paediatric study 105MS306. This update to Plegridy Product Information implements the outcome of the assessment of procedure EMA/PAM/0000245467 wherein the study was assessed previously.

Study 105MS306 is an open-label, randomized, active-controlled study to evaluate the safety, tolerability and efficacy of BIIB017 with the active control interferon beta-1a (Avonex) in paediatric subjects aged 10 - < 18 years with RRMS. 152 patients were randomised in a 1:1 ratio to treatment with BIIB017 125 µg SC every 2 weeks or interferon beta-1a administered at a dose of 30 µg IM injection once weekly.

An interim analysis of Part 1a data was conducted after all participants completed Week 48 (n= 124). The primary endpoint was the adjusted annualized relapse rate (ARR) 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 main secondary endpoint at week 48, was the number of participants free of new or newly enlarging T2 hyperintense lesions on brain MRI scans. At week 48, 0.136 (95% CI: 0.064, 0.243) participants in BIIB017 were free of new or newly enlarging T2 hyperintense lesions compared to participants in Avonex group 0.065 (95% CI: 0.018, 0.157). Although the results between the Plegridy and Avonex groups are comparable, the study was not designed as a comparative trial between the treatments (e.g., non-inferiority). Rather the primary objective was to assess the safety and pharmacokinetics with efficacy as exploratory objective. Due to the open-label design, lack of blinding and no comparative analysis between the two treatment groups, the results are considered descriptive.

The results submitted are from an interim analysis and therefore may not fully capture the efficacy (and safety) profile of Plegridy in paediatric patients with RRMS. Thus it is agreed with the MAH to wait until

the results of the study at week 96 are available to discuss a potential extension of the indication. When the results are available, and similar efficacy is (indirectly) observed compared to adult RRMS patients treated with Plegridy, the MAH is recommended to submit an extension of the indication for paediatric patients with RRMS based on paediatric extrapolation (as outlined in ICH11A).

Based on the efficacy and popPK results section 4.2, 5.1 and 5.2 are updated. While the neutral wording of section 5.1 and 5.2 are agreed, the proposed changes to section 4.2 requires some amendment. The MAH proposes to include the statement "*The safety and efficacy of peginterferon beta1a in children and adolescents aged 10 to less than 18 years have not been fully established in multiple sclerosis*". This is not agreed as "fully" may give the assumption that efficacy has been demonstrated to some extent for this patient population, whereas this is not supported by the current available data. The Applicant agrees to amend the PI as requested.

With respect to safety, the most common treatment-emergent adverse events (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%]). Most adverse events occurred in similar rate in both treatment groups. Injection site erythema occurred more commonly in the Plegridy group as compared to Avonex (33.3% vs. 7.8%), which may be due to different route of administration of the products (SC vs. IM). Serious adverse events occurred in 13.2% of subjects, and apart from multiple sclerosis relapse occurred only in $\leqslant$2 patients per PT. 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 provided a comparative exercise between the AEs observed in paediatric study 105MS306 and adult study 105MS301. Overall, the most common treatment-emergent adverse events reported for Plegridy in the paediatric population are in line with those reported in adults. Differences in frequencies observed between the adult and paediatric studies may be due to the large difference in sample size (512 vs. 75). The known effects of Plegridy on hematology and blood chemistry in adults were observed also in the current study in children. Based on the provided comparison, there appear to be no new safety risks for Plegridy in paediatric patients. All the relevant safety information is included in section 4.8 of the Plegridy SmPC.

The benefit-risk balance of Plegridy 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 sections 4.2, 4.8, 5.1 and 5.2 of the SmPC based on interim results from study 105MS306. This is 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. The PL is updated accordingly.

☒ is recommended for approval.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan PIP EMEA-001129-PIP01-11-M06 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet (PL).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es)I and IIIB 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

Sections 5.1, 5.2, and 4.8 are updated to inform about study design features of the randomised, open-label active-controlled (interferon beta-1a) parallel group study in patients with RRMS aged 10 to less than 18 years of age (section 5.1) and main pharmacokinetics (section 5.2), efficacy (section 5.1) and safety (section 4.8) results in this study.

Section 4.2 is updated to inform that in spite of the above information, the safety and efficacy of peginterferon beta1a in children and adolescents have not been established in multiple sclerosis

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

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

5. Introduction

Plegridy (peginterferon beta-1a, BIIB017) is currently authorisated for the treatment of relapsing-remitting MS (RRMS) in adults. The purpose of this variation is to update the Plegridy Product Information based on 1-2 year interim paediatric data available from the 4 year ongoing Study 105MS306. This is an open-label, randomized, active-controlled study to evaluate the safety, tolerability and efficacy of BIIB017 in pediatric subjects aged 10 - < 18 years with RRMS.

The data was submitted previously in EMA/PAM/0000245467, where the outcome was to submit a type II variation to allow for an update to the Product Information.

6. Clinical Pharmacology aspects

6.1. Methods – analysis of data submitted

In study 105MS306 (see for more information on study design etc. section 7), sparse sampling was conducted in pediatric participants. A popPK approach was used to characterize the PK of BIIB017 in pediatric RRMS participants aged 10 to <18 years.

To be noted, a popPK model was originally established using data from adult healthy and RMS participants. In the pivotal Phase 3 study 105MS301, 1512 participants were randomized with a ratio of approximately 1:1:1 into 3 treatment groups: placebo, BIIB017 125 µg Q2W, and BIIB017 125 µg Q4W. BIIB017 or placebo was administered SC. The final popPK model was a one-compartment linear model with a first-order absorption rate. Body mass index was identified as a significant covariate on CL/F and V/F.

In study 105MS306, PK samples were collected for BIIB017 on Day 1, Week 4, and Week 24 visits. On Day 1 after the first dose and on Day 1 of Week 24, PK samples were collected within 8 hours of dosing. For Week 4, Day 1, PK sampling for BIIB017 was to occur within 8 hours after dosing, on Day 3 at 48 ± 12 hours (optional home visit for sampling, where available), and on Day 6 at 120 ± 24 hours (optional home visit for sampling, where available).

All samples were analyzed using a validated ELISA method (VeriKine-HS Human Interferon Beta Serum ELISA kit) with lower limit of quantitation of 15.6 pg/ml. PPK analysis was conducted to characterize the PK of BIIB017 in the pediatric participants. The individual parameter estimates from the final PPK model were used to generate simulated steady-state exposure metrics ($AUC_{0\text{-}tau}$, C_{max}, C_{trough}, and t_{max}) for all pediatric RRMS participants receiving the approved adult dose of 125 µg Q2W via SC administration.

The PK analysis set included all participants who received at least 1 dose of BIIB017 treatment in Part 1 and had at least 1 measurable drug concentration postbaseline. A total of 306 measurable PK observations were collected from 75 participants from study 105MS306. One participant was excluded from the analysis due to being non-evaluable (i.e., no measurable PK observations). BLQ observations after administration of the first dose (post-treatment BLQ) account for 4.6% of all observations. These BLQ samples were excluded from the popPK analysis, which was deemed appropriate (< 5% of all observations). No other measurable PK data were excluded. Consequently, the final popPK analysis dataset consisted of 74 participants and 292 PK observation records. The popPK report has been already submitted previously (EMA/PAM/0000245467).

6.2. Results

For the popPK analysis, the existing popPK model for BIIB017 based on the adult PK data from study 105MS301 was evaluated using a validation VPC approach for its robustness in describing the data from pediatric participants in study 105MS306. Results showed that the popPK model underpredicted the observed BIIB017 plasma concentrations from the pediatric RRMS population. Therefore, model refinements were necessary to improve model fit of the data from pediatric participants. To conduct model refinements, the PK analysis dataset, which included data from study 105MS306, was combined with the prior PK data from adults. The refined final popPK model included a newly added covariate for population effect (pediatric versus adult) on CL/F and V/F. As indicated by the applicant, the refined model showed improved fit and robustness, as confirmed by VPC and nonparametric bootstrap, in describing the PK data from pediatric participants in study 105MS306. Pediatric participants (10 to < 18 years old) with RRMS were estimated to have about 56% lower CL/F and 46% lower V/F as compared with adult participants with MS.

The individual parameter estimates from the refined final popPK model were used to generate simulated steady-state exposure metrics ($AUC_{0\text{-}tau}$, C_{max}, and C_{trough}) for all adult and pediatric MS participants in the popPK analysis dataset receiving the 125 µg Q2W dose. The steady-state exposure values of adults and pediatrics, including C_{max}, C_{trough}, $AUC_{0\text{-}tau}$ and t_{max} are listed in table 1. Simulation results showed that individual pediatric exposures were highly overlapping with the individual adult exposures (figure 1), even though mean steady-state $AUC_{0\text{-}tau}$ in pediatric RRMS participants was about 2.5 times higher than in adult MS participants (figure 2). This was consistent with the estimated lower CL/F in pediatric participants. Similarly, simulated steady-state C_{max} and C_{trough} were higher in pediatric RRMS participants as compared with adult MS participants. Furthermore, among pediatric RRMS participants, exposure was similar between the age categories of 10 to < 13 years (n=7) and 13 to < 18 years (n=67). The steady-state t_{max} values are, in general, comparable between adults and pediatrics. The reason for relatively higher predicted exposure in pediatric participants might be due to higher bioavailability in the pediatric participants leading to lower CL/F and V/F. However, due to sparse PK sampling, this could not be confirmed in the current PPK analysis.

Additionally, out of 75 participants randomized to the BIIB017 group, 29 participants (38.7%) were tested positive for anti–IFN β-1a antibodies and only 2 participants (2.7%) of them were tested positive for neutralizing IFN β-1a antibodies. The incidence of participants with neutralizing IFN β-1a antibodies in the BIIB017 group was low and at nonpersistent levels. There was no apparent impact on safety or clinical efficacy, although the analysis was limited by the low incidence of immunogenicity (CSR 105MS306, Section 12.6). The low incidence and nonpersistent level of neutralizing antibody was also not considered to have any meaningful effect on the PK.

Table 1. Simulated steady-state exposure metrics

	Adults (N = 1453)	Pediatrics (N = 74)	10 to <13 years (N=7)	13 to <18 years (N=67)
$AUC_{0\text{-}tau}$ (hr•ng/mL)				
Mean (SD)	39.7 (11.7)	101 (49.1)	96.4 (28.3)	101 (50.9)
Median [Min, Max]	38.0 [20.2, 130]	90.1 [29.2, 237]	101 [61.4, 133]	90.0 [29.2, 237]
	Adults (N = 1453)	**Pediatrics (N = 74)**	**10 to <13 years (N=7)**	**13 to <18 years (N=67)**
C_{max} (pg/mL)				
Mean (SD)	280 (70.5)	647 (278)	808 (368)	630 (265)
Median [Min, Max]	272 [107, 767]	590 [186, 1490]	775 [374, 1490]	586 [186, 1380]
C_{trough} (pg/mL)				
Mean (SD)	31.1 (24.0)	109 (102)	56.1 (31.2)	114 (105)
Median [Min, Max]	27.0 [0.342, 291]	74.2 [0.429, 469]	58.5 [5.88, 92.0]	84.8 [0.429, 469]
T_{max} (hour)				
Mean (SD)	15.9 (0.833)	16.4 (1.60)	15.3 (1.60)	16.5 (1.57)
Median [Min, Max]	16.0 [11.0, 21.0]	16.0 [11.0, 19.0]	16.0 [12.0, 17.0]	16.0 [11.0, 19.0]
CL/F (L/hr)				
Mean (SD)	3.34 (0.755)	1.55 (0.772)	1.40 (0.436)	1.57 (0.799)
Median [Min, Max]	3.29 [0.781, 6.17]	1.39 [0.515, 4.27]	1.24 [0.941, 2.04]	1.39 [0.515, 4.27]
V/F (L)				
Mean (SD)	469 (132)	260 (141)	180 (98.2)	268 (142)
Median [Min, Max]	450 [131, 2110]	222 [681, 793]	152 [68.1, 373]	245 [80.0, 793]
Ka (hr-1)				
Mean (SD)	0.21 (0.0019)	0.21 (0.0037)	0.22 (0.0039)	0.21 (0.0036)
Median [Min, Max]	0.21 [0.21, 0.23]	0.21 [0.21, 0.23]	0.22 [0.21, 0.22]	0.21 [0.21, 0.23]

Source: BIOG-PMX-BIIB017-6589_Pediatric_Exposures_Oct2024_v7.Rmd

Abbreviations: $AUC_{0\text{-}tau}$=area under the plasma concentration-time curve over 1 dosing interval; C_{max}=maximum concentration; C_{trough}=trough concentration; T_{max}=time to maximum concentration; CL/F=apparent clearance; V/F=apparent volume of distribution; K_a=absorption rate; Max=maximum; Min=minimum; N=number of subjects; SD=standard deviation

Figure 1. Simulated steady-state pharmacokinetic profile of adult and pediatric MS participants (semi-logarithmic scale)

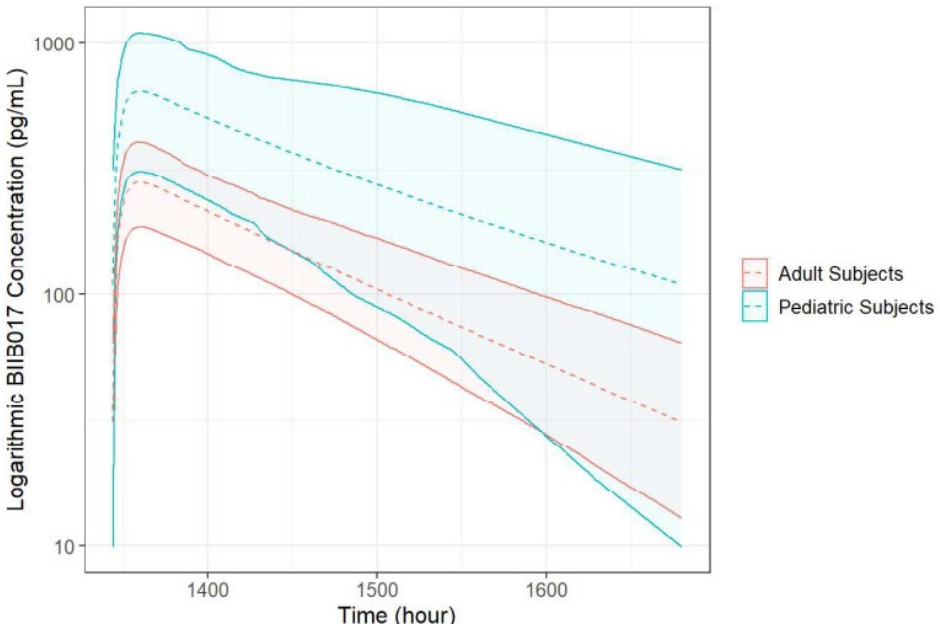
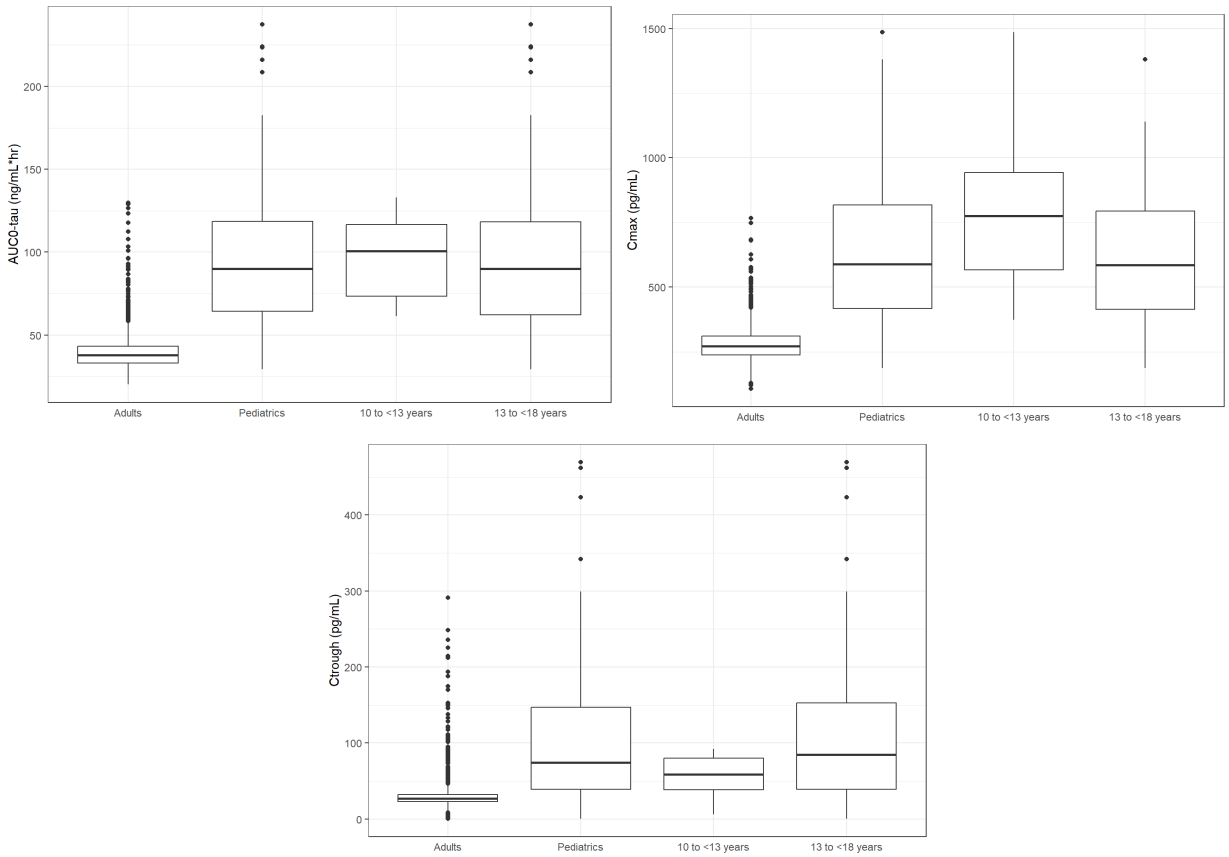


Figure 2. Predicted adult versus pediatric steady-state exposure of BIIB017 in MS participants



Note: Adults (n=1453), pediatrics (n=74), age group = 10 to < 13 years (n=7), age group = 13 to < 18 years (n=67).

6.3. Discussion

The simulated individual steady-state exposures in pediatric RRMS participants were overlapping with the simulated individual adult steady-state exposures, however, the mean simulated $AUC_{0\text{-}tau}$ in pediatric RRMS participants was about 2.5 times higher than in adult RRMS participants. This was consistent with the estimated lower apparent clearance in pediatric participants. Among the pediatric participants, exposures were comparable between participants aged 10 to < 13 years and those aged 13 to < 18 years. For the safety and efficacy aspects, reference is made to the sections below.

Based upon the obtained results in pediatric subjects, a paragraph was added to section 5.2 of the SmPC to include the results of the popPK analysis. The results have been appropriately worded.

7. Clinical Efficacy aspects

Study 105MS306 is a multiple-part study consisting of Part 1 (Part 1a and Part 1a + Part 1b) and Part 2. An interim analysis of the study with cut of data 24 August 2024 includes the analysis of Part 1a, i.e. Week 48 evaluation of the safety, tolerability, efficacy and PK of BIIB017 (Plegridy, peginterferon beta-1a) 125 µg SC Q2W in comparison with the active control interferon beta-1a (Avonex) 30 µg IM weekly in paediatric participants aged 10 to < 18 years for the treatment of RRMS.

7.1. 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).

There were 152 participants randomised at a 1:1 ratio to receive treatment with either BIIB017 (125 µg SC Q2W) or Avonex (30 µg IM weekly), including male (n=57) and female (n=95) participants with a median age of 15.5 years in the range of 10 to 17 years. Seventy-seven participants were randomised to receive Avonex, and 75 participants were randomised to receive BIIB017. There were 15 participants randomised to fulfil the PIP requirement of at least 12 evaluable participants for the primary endpoint ages 10 to < 13 years and 137 participants randomised to fulfil the PIP requirement of at least 80 evaluable participants for the primary endpoint ages 13 to < 18 years. Of the 152 participants randomised, 12 participants who were 10 to < 13 years old and 112 participants who were 13 to < 18 years old completed 48 weeks of treatment. Therefore, 124 participants completed 48 weeks of treatment fulfilling the PIP requirement for 100 completers by Week 48.

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 (18 participants [11.8%]; 11 in the Avonex group and 7 in the BIIB017 group), AEs and participant withdrawal (11 participants [7.2%] each; 7 in the Avonex group and 4 in the BIIB017 group), and parent/guardian withdrawal (7 participants [4.6%]; 3 in the Avonex group and 4 in the BIIB017 group).

As of the data cutoff date, 47 participants (30.9%) were withdrawn from the study, 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%]; 11 in the Avonex group and 5 in the BIIB)17 group), participant withdrawal (12 participants [7.9%]; 8 in the Avonex group and 4 in the BIIB017 group), AEs (9 participants [5.9%]; 6 in the Avonex group and 3 in

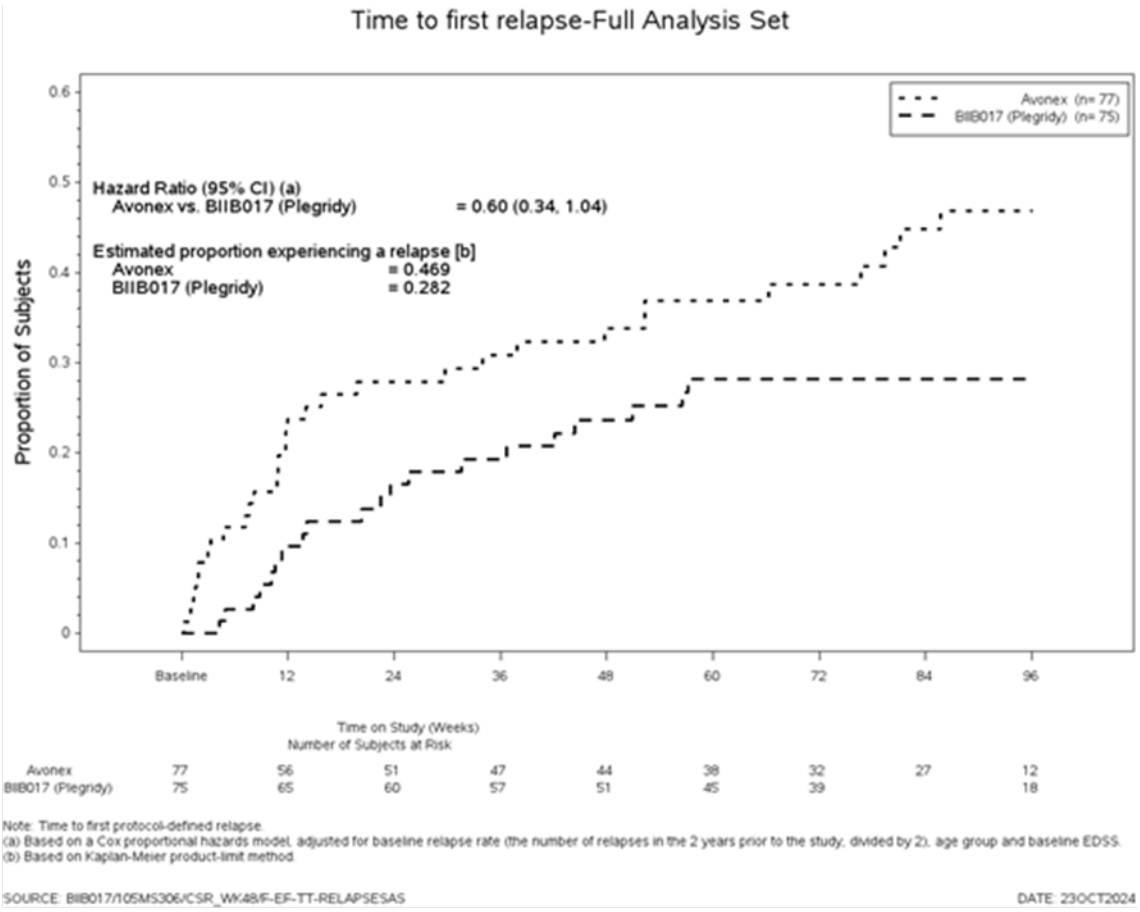
the BIIB017 group), and parent/guardian withdrawal (7 participants [4.6%]; 3 in the Avonex group and 4 in the BIIB017 group).

7.2. Results

The primary endpoint of this study was to assess annualized relapse rate (ARR) at Week 48. In the full analysis set 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. 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.

For the time to first relapse and proportion of participants free of relapse, 53 participants (34.9%) experienced a relapse: 32 participants (41.6%) in the Avonex group and 21 participants (28.0%) in the BIIB017 group. The hazard ratio (BIIB017/Avonex) was 0.609 (95% CI: 0.35, 1.06). 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 0.712 overall, 0.662 in the Avonex group, and 0.764 in the BIIB017 group.

Figure 3. Time to first relapse – full analysis set



The number of participants with data available for brain MRI scans at Baseline and Week 48 was 128: 62 participants in the Avonex group and 66 in the BIIB017 group. The overall proportion of participants free of new or newly enlarging T2 hyperintense lesions relative to baseline was 0.102 (95% CI: 0.055,

0.67), of which 0.065 (95% CI: 0.018, 0.157) were in the Avonex group and 0.136 (95% CI: 0.064, 0.243) were in the BIIB017 group. At Week 48, the overall proportion of participants free of new MRI activity relative to baseline was 0.102 (95% CI: 0.055, 0.167): 62 participants in the Avonex group (0.065; 95% CI: 0.018, 0.157) and 66 participants in the BIIB017 group (0.136; 95% CI: 0.064, 0.243).

The adjusted mean (95% CI) number of new or newly enlarged T2 hyperintense lesions relative to baseline 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.

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 Baseline, the overall mean (SD) number of Gd-enhancing lesions was 2.14 (4.10) in the Avonex group and 2.24 (4.12) 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 4.6 (8.45) in the Avonex group and 1.3 (8.51) in the BIIB017 group.

At Week 48, the mean (SD) change from baseline in EDSS score was 0.00 (0.962) in the Avonex group and 0.15 (0.769) in the BIIB017 group. At Week 96, the mean change from baseline in EDSS score was -0.10 (0.682) in the Avonex group and 0.03 (0.695) in the BIIB017 group.

PedsQL scale scores were determined every 24 weeks, starting at Baseline. Overall, mean scores in each dimension were similar between Avonex and BIIB017 treatment groups, with mean scores within 1 SD, except for the Work/School dimension.

For the exploratory endpoints, progression of disability occurred in 6 participants (8%) in the Avonex group and 4 participants (5%) 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 0.544 (95% CI: 0.152, 1.948).

7.3. Discussion

The efficacy data of study 105MS306 has been previously assessed in an article 46 procedure (EMA/PAM/0000245467).

Briefly, the study design was considered a conventional study in RRMS in terms of duration and endpoints. 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.

In the clinical overview, the MAH concludes that "*No efficacy conclusions can be drawn from this open-label study, since a comparative inferential assessment to evaluate the primary efficacy endpoint was not included. Therefore, no recommendation on the use of BIIB017 in the paediatric populations has been made.*".

It is acknowledged that the study was not designed as a comparative trial between Plegridy and Avonex (e.g. non-inferiority), rather the primary objective was to assess the safety and pharmacokinetics with efficacy as exploratory objective. In addition, the results submitted are from an interim analysis and therefore may not fully capture the efficacy (and safety) profile of Plegridy in paediatric patients with RRMS.

The proposed wording in the section 5.1 of the Plegridy SmPC adequately describes the available information.

As also discussed previously in the Article 46 procedure, Study 105MS306 is insufficient to support a claim of efficacy of Plegridy in paediatric patients with RRMS in light of the methodological issues identified (e.g. open label design etc.). In addition, the current submitted data are part of an interim analysis, with more data will become available when the study has been finalized. Hence, these data preclude a recommendation for a paediatric posology in section 4.2 of the Plegridy SmPC. The MAH proposes to include the statement "*The safety and efficacy of peginterferon beta1a in children and adolescents aged 10 to less than 18 years have not been fully established in multiple sclerosis*". This is not agreed as "fully" may give the assumption that efficacy has been demonstrated to some extent for this patient population, whereas this is not supported by the current available data. Therefore, the MAH should remove "fully" from the proposed wording in section 4.2. The MAH agrees to amend the PI as requested.

8. Clinical Safety aspects

8.1. Study 105MS306

In Study 105MS306 Part 1a, 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 TEAEs, 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, 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.

The most common SAE in both groups was multiple sclerosis relapse, which reflects MS disease activity.

Clinical laboratory assessments, vital signs, and ECG evaluations were consistent with the known safety profile of BIIB017. With respect to immunogenicity, 57/150 (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 neutralising 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 neutralising 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.

8.2. Post hoc analysis – comparison with adult data

The following post hoc safety analysis was performed to provide further insight into the safety profile of BIIB017 in the paediatric population compared with the adult population.

Overview of Paediatric and Adult Safety Outcomes in BIIB017 Studies

Table 2 summarises comparative safety events from Study 105MS306 (Part 1a, through Week 48) in paediatric participants and the controlled BIIB017 Study 105MS301 in adult participants receiving BIIB017 Q2W through Week 48 .

In general, the frequency and types of TEAEs were consistent between the two populations. Any differences in reported frequencies should be interpreted with caution due to the smaller sample size of the paediatric population (N=75) and the open-label nature of the study.

Flu-like symptoms and injection site reactions are known side effects of BIIB017 treatment. The most commonly reported TEAE PTs in the SOC General disorders and administration site conditions in Study 105MS306 Part 1a were similar to those reported in the pivotal clinical Study 105MS301. These TEAEs included injection site erythema, influenza like illness and pyrexia. In Study 105MS301, most TEAEs associated with flu-like symptoms and injection site reactions were mild or moderate in severity. In Study 105MS306 Part 1a, all TEAEs in the SOCs General disorders and administration site conditions and Musculoskeletal and connective tissue disorders were mild or moderate in severity. No BIIB017 participants discontinued study treatment in Study 105MS306 Part 1a because of TEAEs in these SOCs.

In Study 105MS306 Part 1a, TEAEs of alanine aminotransferase increased, aspartate aminotransferase increased, and gamma-glutamyltransferase increased were consistent with the known hepatic enzyme elevations associated with BIIB017 treatment. Like the adult population, most hepatic enzyme elevations were <3 x ULN. In Study 105MS301, elevations of ALT and AST (>5 × ULN) were reported in 2% and <1% of adults treated with BIIB017, respectively. In Study 105MS306 Part 1a, elevations of ALT and AST >5 × ULN were reported in 1 participant (1%) and in no participants treated with BIIB017, respectively, up to Week 48. No participants had laboratory data corresponding to Hy's law in Study 105MS306 Part 1a as of the data cutoff.

Table 2. Comparative safety: study 105MS306 (part 1a, through week 48) and Plegridy adult data

SOC/PT	**Plegridy 105MS306 Part 1**		**Plegridy Adult**	
	BIIB017 Q2 weeks (N=75) %	**Frequency Category[1]**	**BIIB017 Q2 weeks (N = 512) %**	**Frequency Category**
Nervous System Disorders				
Headache	17.3%	Very common	44%	Very Common
Gastrointestinal Disorders				
Nausea	2.7%	Common	9%	Common
Vomiting	6.7%	Common	5%	Common
Musculoskeletal and Connective Tissue Disorders				
Myalgia	4.0%	Common	19%	Very Common
Arthralgia	4.0%	Common	11%	Very Common
General disorders and administration site conditions				
Injection site erythema	32.0%	Very Common	62%	Very Common
Influenza like illness	20.0%	Very Common	47%	Very Common
Pyrexia	14.7%	Very Common	45%	Very Common
Chills	0%	-	17%	Very Common
Injection site pain	2.7%	Common	15%	Very Common
Asthenia	5.3%	Common	13%	Very Common
Injection site pruritus	1.3%	Common	13%	Very Common
Hyperthermia	5.3%	Common	4%	Common
Pain	0%	-	5%	Common
Injection site oedema	0%	-	3%	Common
Injection site warmth	0%	-	3%	Common

Injection site haematoma	4.0%	Common	3%	Common
Injection site rash	0%	-	2%	Common
Investigations				
Body temperature increased	1.3%	Common	6%	Common
Alanine aminotransferase (ALT) increased	10.7%	Very Common	6%	Common
Aspartate aminotransferase (AST) increased	5.3%	Common	4%	Common
Gamma-glutamyltransferase (GGT) increased	2.7%	Common	3%	Common
Skin and Subcutaneous Tissue Disorders				
Pruritus	0%	-	4%	Common

Source: CSR 105MS306 (Part 1, through week 48) and Plegridy Investigator's Brochure, Version 15
[1]Frequencies were defined as follows: Very common (≥ 1/10), Common (≥ 1/100 to < 1/10).

In summary, the post hoc comparative safety analysis demonstrates that the safety and tolerability profile of BIIB017 in paediatric participants is consistent with the established adult safety profile. No new safety signals were identified, and the observed numerical differences in adverse event frequencies do not represent clinically relevant distinctions between populations.

Paediatric and Adult Leukocyte Counts in Plegridy Studies

Decreased peripheral blood counts, including decreases in leukocytes, have been reported in patients receiving BIIB017 and other interferons. Overall, the WBC dynamics in the Study 105MS306 Part 1a population were similar to those observed in the adult population from 105MS301. In both Study 105MS306 Part 1a and 105MS301, the mean leukocyte counts decreased over 48 weeks but remained within normal limits. In Study 105MS306 Part 1a, the mean leukocyte counts decreased by 9.61% from baseline at Week 48 in the BIIB017 Q2W group. In Study 105MS301, the mean leukocyte counts decreased by approximately 9% from baseline in the BIIB017 Q2W group at Week 48.

In Study 105MS306, decreases in WBC counts of $<3.0 \times 10^9$/L were observed in 12% of patients receiving BIIB017 Q2W over 96 weeks. In 105MS301, decreases in WBC counts of $<3.0 \times 10^9$/L were observed in 7% and 10% of patients receiving BIIB017 Q2W in Year 1 and Year 2, respectively.

The slight numerical differences in WBC between the two studies are likely explained by relatively small numbers of participants in Study 105MS306 Part 1a and are not considered meaningful. No participants in study 105MS306 Part 1a experienced severe or serious TEAEs associated with decreases in WBC counts.

8.3. Real world safety data

Cumulative to 12 May 2025, a search of the global safety database for BIIB017 in cases <17 years of age revealed 1891 events in 700 case reports. Of the 1891 events, 576 events (30%) were confirmed by health care professionals (HCPs), and 1315 events (70%) were reported by consumers. The majority of events (1823 events; 96%) were nonserious. Solicited reports constituted the predominant source of reports (76% of events), followed by spontaneous reports (22%) and noninterventional studies (2%). The most commonly reported events were off-label use (301 events; 15.9% of total events), product

administered to patient of inappropriate age (230 events; 12.2%), injection site erythema (81 events; 4.3%), influenza like illness (74 events; 3.9%), drug delivery system malfunction (73 events; 3.9%), headache (63 events; 3.3%), pyrexia (47 events; 2.5%), fatigue (46 events; 2.4%), product dose omission issue (39 events; 2.1%), and multiple sclerosis relapse (34 events; 1.8%). The most reported serious event was MS relapse (16 events; out of total 68 serious events). Overall, the findings are consistent with the known safety profile for BIIB017.

8.4. Discussion

The safety data of study 105MS306 has been previously assessed in an article 46 pdWS (EMA/PAM/0000245467).

Summarising, most adverse events occurred in similar rate in both treatment groups. Injection site erythema occurred more commonly in the Plegridy group as compared to Avonex (33.3% vs. 7.8%), which may be due to different route of administration of the products (SC vs. IM). Serious adverse events occurred in 13.2% of subjects, and apart from multiple sclerosis relapse occurred only in ≤2 patients per PT. 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 provided a comparative exercise between the AEs observed in paediatric study 105MS306 and adult study 105MS301. Overall, the most common treatment-emergent adverse events reported for Plegridy in the paediatric population are in line with those reported in adults. Differences in frequencies observed between the adult and paediatric studies may be due to the large difference in sample size (512 vs. 75). The known effects of Plegridy on hematology and blood chemistry in adults were observed also in the current study in children. Based on the provided comparison, there appear to be no new safety risks for Plegridy in paediatric patients.

In addition, a search was conducted in the Plegridy global safety database for case reports in paediatric patients (< 17 years). Of the 700 reports, the most common reported events were related to off label use ("off label use" 15.9% and "product administered to patient of inappropriate age" 12.2%). The remainder of the events reported are in line with the safety profile observed in study 104MS306 and the established safety profile of Plegridy in adults (e.g. influence, injection site erythema, pyrexia etc.).

All the relevant safety information is included in section 4.8 of the Plegridy SmPC.

9. PRAC advice

Not Applicable

10. Changes to the Product Information

As a result of this variation, section(s) 4.2, 4.8, 5.1 and 5.2 of the SmPC are being updated to include the results from study 105MS306. The Package Leaflet (PL) is updated accordingly.

Please refer to Attachment 1 which includes all proposed changes to the Product Information.

11. Request for supplementary information

11.1. Major objections

Not Applicable

11.2. Other concerns

Clinical aspects

1. The MAH is requested to discuss the data to support a paediatric posology and suitability of these data to allow extrapolation of the adult findings in RRMS to RRMS patients aged 10-18 taking into account the natural history course of RRMS in both children and adults and the observed RMI effects at week 48 and 96.

2. The MAH is recommended to amend the proposed text in section 4.8 of the Plegridy SmPC as follows:

   Paediatric population

   The safety of peginterferon beta-1a in paediatric patients aged 10 to less than 18 years was studied in an open-label randomized active controlled paediatric trial with 152 paediatric patients with RRMS (peginterferon beta-1a n=75; interferon beta-1a n=77). 66 patients in the peginterferon beta-1a group completed 48 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 safety profile in paediatric patients receiving peginterferon beta-1a was consistent with that observed in adult patients.*~~

3. The MAH is requested to propose an update of the Package Leaflet based on the SmPC and in line with Avonex, or to justify why such update is not considered appropriate for Plegridy.

12. Assessment of the responses to the request for supplementary information

12.1. Major objections

None

12.2. Other concerns

Clinical aspects

Question 1
The MAH is requested to discuss the data to support a paediatric posology and suitability of these data to allow extrapolation of the adult findings in RRMS to RRMS patients aged 10-18 taking into account the natural history course of RRMS in both children and adults and the observed RMI effects at week 48 and 96.

Summary of the MAH's response

While the pathophysiology of RRMS appears broadly consistent across age groups, the higher relapse rate and MRI lesion burden in paediatric patients may influence treatment response dynamics. Genetic, serum, CSF, and cell-based studies largely support a shared biology between paediatric-onset and adult-onset disease. However, clinically paediatric onset MS is generally characterized by more frequent relapses and MRI activity compared to adult-onset disease.

The exposure-response relationship for interferon beta-1a has not been fully characterized in paediatric patients, limiting the ability to confidently extrapolate efficacy from adult data. In addition, the adult studies with Plegridy have a different study design and comparators which makes comparisons or extrapolations from adult data difficult. Given the clinical differences and different study designs direct comparisons and extrapolations are limited.

The safety profile of Plegridy in the paediatric population observed in the CHARGE study appears generally consistent with the known safety profile of Plegridy in adults with RRMS. However, meaningful comparisons of efficacy between paediatric and adult populations are limited by differences in the clinical course of paediatric multiple sclerosis, as well as by the design and interim results of the CHARGE study.

While regulatory frameworks support extrapolation in paediatric populations under certain conditions, the current evidence base for Plegridy in paediatric RRMS does not yet meet the threshold for full extrapolation due to the differences in disease activity, study design, and limited efficacy data. Paediatric MS is characterized by a more active disease course compared to adults ([Gorman 2009]; [Benson 2014]; [Waldman 2016]). Furthermore, in the interim analysis of the CHARGE study, there were no meaningful differences identified in efficacy between Avonex and Plegridy in paediatric patients. Complete dataset from the CHARGE study, expected at Week 96, may offer further insight into the potential benefit of Plegridy in this population.

References

Benson LA, Healy BC, Gorman MP, et al. Elevated relapse rates in pediatric compared to adult MS persist for at least 6 years. Mult Scler Relat Disord. 2014;3(2):186-93.

Gorman MP, Healy BC, Polgar-Turcsanyi M, et al. Increased relapse rate in pediatric-onset compared with adult-onset multiple sclerosis. Arch Neurol. 2009;66(1):54-9.

Waldman A, Ness J, Pohl D, et al. Pediatric multiple sclerosis: Clinical features and outcome. Neurology. 2016;87(9 Suppl 2):S74-81.

Assessment of the MAH's response

The MAH's argumentation that there are differences in disease activity and study design prohibiting readily/ full extrapolation of Plegridy from adults to paediatric patients with RRMS is acknowledged.

However, partial extrapolation of efficacy obtained in adult patients with RRMS to paediatric patients with RRMS has been achieved previously (Tecfidera, EMEA/H/C/002601/II/0073).

For Tecfidera, a similar study was submitted as in the current procedure, i.e., a 96 week open-label study that evaluated Tecfidera against Avonex, in paediatric patients with RRMS aged 10 - < 18 years. Although the study showed comparable efficacy of Tecfidera in paediatric patients (indirectly) compared to adults (randomized, placebo-controlled studies), in light of the methodological shortcomings (open-label design etc.), the study could not provide stand-alone confirmation of efficacy. Consequently, paediatric extrapolation was applied and the CHMP concluded that extrapolation of efficacy from adults with RRMS to paediatric patients aged > 13 years was feasible based on *"… shared disease biology, similar exposure (derived from PK studies), and similar anti-inflammatory effects. Re-establishing efficacy on its own is not necessary*." (Tecfidera EPAR, p. 96-97). No exposure-response modelling was submitted as support for extrapolation and similarity in exposure was deemed sufficient.

Hence, disease similarity and differences in study designs between adult and paediatric patients with RRMS have already been accepted by the CHMP in 2022. Considering the similarities between the

Plegridy paediatric development program and Tecfidera, it is anticipated that the same principles would be applied if the MAH would seek partial extrapolation of efficacy.

It is agreed with the MAHs argument that the interim analysis may not fully capture the efficacy (and safety) profile of Plegridy in paediatric patients with RRMS. Thus it is agreed with the MAH to wait until the results of the study at week 96 is available. When these results are available, and similar efficacy is (indirectly) observed compared to adult RRMS patients treated with Plegridy, the MAH is recommended to submit an extension of the indication for paediatric patients with RRMS based on paediatric extrapolation (as outlined in ICH11A).

As also discussed previously in the article 46 procedure, Study 105MS306 is insufficient to support a claim of efficacy of Plegridy in paediatric patients with RRMS in light of the methodological issues identified (e.g. open label design etc.). In addition, the current submitted data are part of an interim analysis, with more data becoming available when the study has been finalized. These data preclude a recommendation for a paediatric posology in section 4.2 of the Plegridy SmPC. The MAH proposes to include the statement "*The safety and efficacy of peginterferon beta1a in children and adolescents aged 10 to less than 18 years have not been fully established in multiple sclerosis*". This is not agreed as "fully" may give the assumption that efficacy has been demonstrated to some extent for this patient population, whereas this is not supported by the current available data. Therefore the MAH should remove "fully" from the proposed wording in section 4.2 (**2nd RfSI**).

Conclusion

Issue is not pursued further, but an update to section 4.2 of the SmPC and corresponding information in the PL is needed (see 2nd request).

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

No need to update overall conclusion and impact on benefit-risk balance

Question 2

The MAH is recommended to amend the proposed text in section 4.8 of the Plegridy SmPC as follows:

Paediatric population

The safety of peginterferon beta-1a in paediatric patients aged 10 to less than 18 years was studied in an open-label randomized active controlled paediatric trial with 152 paediatric patients with RRMS (peginterferon beta-1a n=75; interferon beta-1a n=77). 66 patients in the peginterferon beta-1a group completed 48 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 safety profile in paediatric patients receiving peginterferon beta-1a was consistent with that observed in adult patients.*~~

Summary of the MAH's response

The MAH has updated the text in section 4.8 as proposed by the rapporteur and consequential update to Package Leaflet section 4 is also proposed as part of this response submission.

Assessment of the MAH's response

The MAH has updated the SmPC as requested.

Conclusion

Issue resolved

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

No need to update overall conclusion and impact on benefit-risk balance

Question 3
The MAH is requested to propose an update of the Package Leaflet based on the SmPC and in line with Avonex, or to justify why such update is not considered appropriate for Plegridy.

Summary of the MAH's response
The MAH has proposed update to the Package Leaflet in sections 2 and 4, based on the SmPC and in line with Avonex.

Assessment of the MAH's response
The MAH has updated the Package Leaflet as requested.

Conclusion

Issue resolved

Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

13. 2nd Request for supplementary information

13.1. Major objections

None

13.2. Other concerns

Clinical aspects

1. As also discussed previously in the article 46 procedure, Study 105MS306 is insufficient to support a claim of efficacy of Plegridy in paediatric patients with RRMS in light of the methodological issues identified (e.g. open label design etc.). In addition, the current submitted data are part of an interim analysis, with more data becoming available when the study has been finalized. These data preclude a recommendation for a paediatric posology in section 4.2 of the Plegridy SmPC. The MAH proposes to include the statement "The safety and efficacy of peginterferon beta1a in children and adolescents aged 10 to less than 18 years have not been fully established in multiple sclerosis". This is not agreed as "fully" may give the assumption that efficacy has been demonstrated to some extent for this patient population, whereas this is not supported by the current available data. Therefore the MAH should remove "fully" from the proposed wording in section 4.2.

   The corresponding PIL wording needs to be amended accordingly, i.e., the MAH is requested to amend the wording in section 3 of the PL as follows:

   Children and adolescents
   ~~Plegridy is not recommended for use in children and adolescents because there is limited data on the use of Plegridy in this population.~~ Plegridy should not be used in children <u>and adolescents</u> ~~below~~

~~10 years of age~~ because it is yet to be established whether it would work for them and whether it would be safe.

Assessment of the responses provided before the adoption of the RSI

On 5 December 2025, the Applicant provided updated PI version including the above requested amendments in section 4.2 of the SmPC and PL.

Issue solved without the need for an adoption of a 2nd RSI.