Amsterdam, 22 June 2023
EMA/CHMP/313321/2023
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: EMEA/H/C/002827/P46/011

## 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 2023, the MAH submitted an uncompleted paediatric study (800MS301) for Plegridy (peginterferon ß-1a), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are not submitted as part of the Paediatric Investigation Plan (PIP).

No short critical expert overview has been provided.

# 2. Scientific discussion

## *2.1. Information on the development program*

Study 800MS301 is a randomised, double-blind, double-dummy, placebo-controlled, 3-arm, parallel-group study in paediatric subjects aged 10 through 17 years to evaluate the efficacy and safety of BG00012 and BIIB017 for the treatment of relapsing-remitting Multiple Sclerosis (RRMS). The study is not part of the agreed Paediatric Investigation Plan (PIP) for Plegridy (EMEA-001129-PIP01-11).

Study 800MS301 was terminated early by the Sponsor due to low recruitment.

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

Plegridy is available as 63 µg /94 µg /125 µg solution for injection in pre-filled syringe or pen, for subcutaneous use. The product is indicated in adult patients with RRMS. The recommended dose of Plegridy is 125 micrograms injected subcutaneously (SC) or intramuscularly (IM) every 2 weeks (14 days). The formulation and dosing in Study 800MS301 were similar to the recommended posology in adults, including initial titration to the target dose. The route of administration in Study 800MS301 was subcutaneous.

## *2.3. Clinical aspects*

### 2.3.1. Introduction

The MAH submitted an abbreviated Clinical Study Report for:

Study 800MS301, a randomised, double-blind, double-dummy, placebo-controlled, 3-arm, parallel-group study in paediatric subjects aged 10 through 17 years to evaluate the efficacy and safety of BG00012 and BIIB017 for the treatment of relapsing-remitting Multiple Sclerosis.

### 2.3.2. Clinical study

***CHMP comment***

Study 800MS301 was terminated early by the Sponsor due to low recruitment. Only 4.2% of the anticipated 260 subjects were recruited at 6 of the planned 50 (global) sites. The study started in the spring of 2019 and was terminated in mid-2022.

The Applicant submitted a Clinical Overview identical to the abbreviated Clinical Study Report.

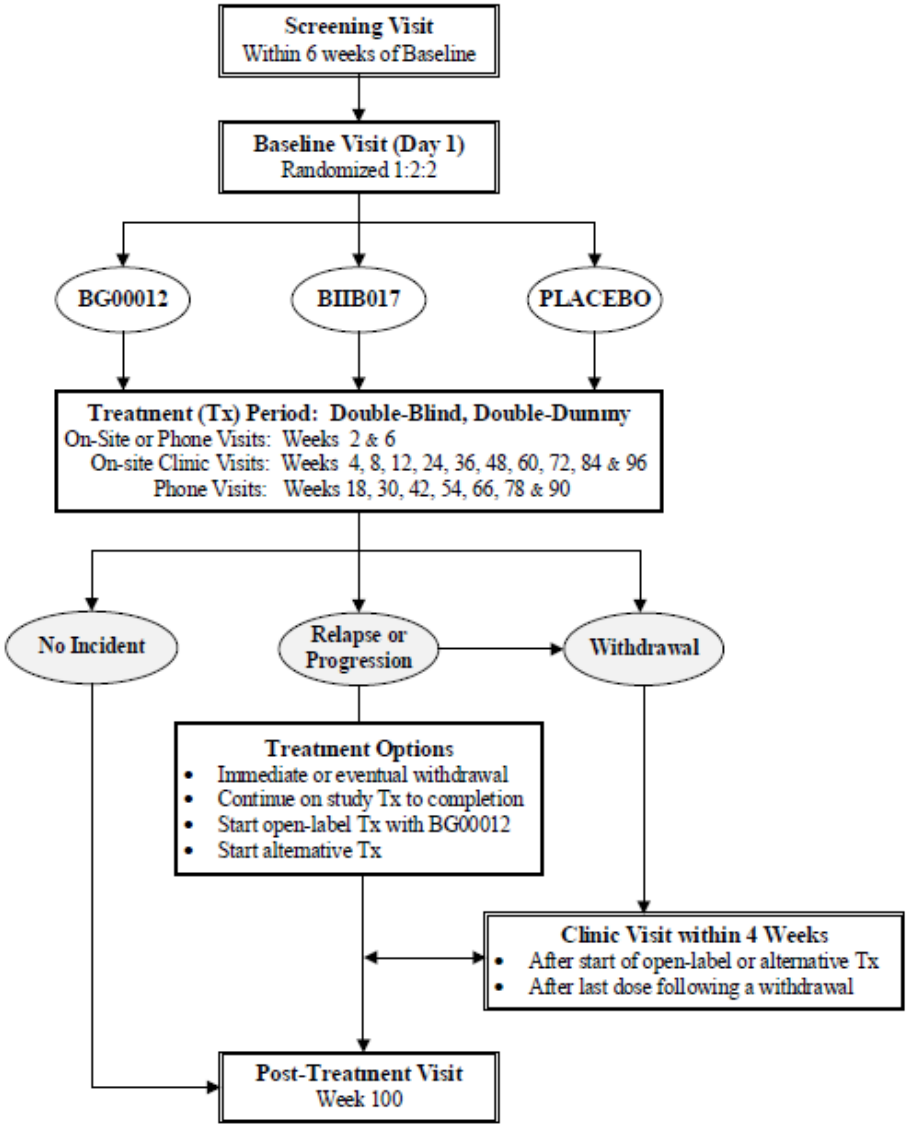
## Study 800MS301

## Description

This was a Phase III randomised, double-blind, double-dummy, placebo-controlled, 3-arm, parallel-group study to evaluate the efficacy and safety of Tecfidera® (BG00012) and Plegridy® (BIIB017) in paediatric subjects 10-17 years of age with relapsing-remitting Multiple Sclerosis (RRMS).

Study duration for each participant was planned to be approximately 106 weeks: a 6-week Screening Period, a 96-week (2 year) Treatment Period, and a 4-week Post-Treatment Period.

**Figure 1: Study Design**




## Methods

### *Study participants*

Main inclusion criteria:

1. Ability of a legally authorised representative (LAR; parent or legal guardian).

2. Aged 10 - 17 years old at the time of informed consent.

3. A diagnosis of RRMS as defined by the revised consensus definition for paediatric multiple sclerosis (MS).

4. An Expanded Disability Status Scale (EDSS) score between 0.0 and 5.0.

5. A body weight of ≥ 30 kg.

6. Experienced ≥ 1 relapse in the 12 months prior to randomisation (Day 1), must have had evidence of asymptomatic disease activity (gadolinium [Gd]-positive lesions) seen on MRI in the 6 months prior to randomisation (Day 1), or must have had ≥ 2 relapses in the 24 months prior to randomisation (Day 1). Relapse was defined as the occurrence of a clinical demyelination event regardless of whether the event was a first (initial) or subsequent (recurrent) demyelinating event.

7. Sexually active participants of childbearing potential had to practice effective contraception during and up to 3 months after the study.

Main exclusion criteria:

1. Primary progressive, secondary progressive, or progressive relapsing MS.

2. Disorders mimicking MS.

3. MS relapse within the 30 days prior to randomisation (Day 1) and/or the participant had not stabilised from a previous relapse prior to randomisation.

4. Any previous treatment with Fumaderm®, Tecfidera, or Plegridy.

5. Treatment with other agents to treat MS symptoms or underlying disease.

***CHMP comment***

The inclusion and exclusion criteria are acceptable.

***Treatments***

Treatment Group 1: BG00012 (Tecfidera) was taken orally at a dose of 120 mg BID for the first 7 days and 2 capsules orally at a dose of 240 mg BID thereafter. The Tecfidera treatment group received a placebo SC injection every 2 weeks on the same schedule as the Plegridy participants.

Treatment Group 2: BIIB017 (Plegridy) was administered SC at a dose of 125 µg Q2W for 96 weeks. In participants receiving Plegridy, drug was titrated to the target dose on the following schedule: 63 µg Plegridy on Day 1, 94 µg Plegridy at Week 2, and 125 µg Plegridy at Week 4. Once participants reached the 125 µg target dose, they were to continue on Plegridy 125 µg SC administered every 2 weeks for the remainder of the study. Plegridy participants received daily placebo capsule(s) on the same schedule as Tecfidera participants.

Treatment Group 3: Placebo participants received a placebo SC injection every 2 weeks and daily placebo capsules according to the titration regimen for the Tecfidera group.

***CHMP comment***

This was a three-arm study with two active treatment groups (Plegridy; Tecfidera) and one placebo group.

The formulation and dosing of Plegridy in Study 800MS301 were similar to the recommended posology in adults, including initial titration to the target dose. The route of administration in Study 800MS301 was subcutaneous only. Adults can also use the product IM.

***Objective(s)***

Primary Objective:

• To evaluate the efficacy of Tecfidera and Plegridy, both compared with placebo, in pediatric participants with RRMS

Secondary Objectives:

• To evaluate the safety and tolerability of Tecfidera and Plegridy

• To assess the effect of Tecfidera and Plegridy, both compared with placebo, on additional clinical and radiological measures of disease activity

Additional Objectives:

• To collect additional safety and efficacy information.

***Outcomes/endpoints***

Primary endpoint (Efficacy)

- Time to first relapse (TTFR)

Secondary endpoints (Safety)

- Occurrence of adverse events (AEs) and serious adverse events (SAEs)
- Number of new or newly enlarging T2 hyperintense lesions on brain magnetic resonance imaging (MRI) scans at Weeks 48 and 96
- Number of Gd-enhancing lesions at baseline and at Weeks 48 and 96
- Annualised relapse rate at Weeks 48 and 96

Additional endpoints

Included [in sum] changes in vital signs, ECGs, clinical laboratory data; growth and development parameters; binding and neutralising antibodies to IFN ß and PEG; depression, changes in T2 hyperintense and T1 hypointense lesions; brain atrophy; fatigue and quality of life (PedsQL™); proportion of disability progressors and time to disability progression.

***CHMP comment***

The primary endpoint of this study is acceptable, although the annual relapse rate (ARR) is more common. Secondary and additional endpoints are also considered acceptable and established endpoints that adequately supplement the primary outcome measure.

***Sample size***

Planned:

Approximately 260 participants, aged 10 to 17 years, inclusive, with a diagnosis of RRMS were planned to be enrolled at approximately 50 sites globally.

Analysed:

At the time the study was terminated, a total of 11 participants had been randomised and dosed.

***Randomisation and blinding (masking)***

To ensure blinding of treatment, a double dummy method was used where both treatment groups received placebo, i.e., the Plegridy treatment group received placebo for Tecfidera, and the Tecfidera treatment group received placebo for Plegridy. The Placebo group received both placebos.

***Statistical Methods***

Study 800MS301 was terminated early. The protocol study plan was changed as reflected in the statistical analysis plan (SAP).

Demographics and Baseline Disease Characteristics

All demographics and baseline disease characteristics were summarised for the intent-to-treat (ITT) Population (all randomised participants who received at least 1 dose of study treatment).

Efficacy

Because the number of participants was limited, no analysis of the TTFR, secondary efficacy endpoints, or exploratory efficacy endpoints was attempted, and therefore, no analysis or statistical summaries were provided. All efficacy data were listed for the ITT Population by treatment group and, for each participant, by visit, and/or by date.

Safety

The Safety Population was defined as all participants who received at least 1 dose of study treatment. Participants were analysed according to the treatment received. Primary safety analysis of AEs, laboratory variables, and vital signs was performed on the Safety Population during the period from the first dose of blinded treatment to the end of blinded treatment.

***CHMP comment***

Due to early study termination, the original statistical plan was abandoned.

***CHMP comment***

In general, Study 800MS301 as originally proposed, was a well-designed study of sufficient length to evaluate the efficacy and safety of Plegridy and Tecfidera in paediatric patients with RRMS. However, these objectives could not be met due to early study termination, as only 4.2% of the anticipated 260 subjects were recruited.

## Results

***Participant flow***

At the time the study was terminated, a total of 11 participants from six sites had been randomised and dosed (2 participants in the Tecfidera group, 6 participants in the Plegridy group, and 3 participants in the placebo group).

One additional participant who was a screen failure was mistakenly randomised before a laboratory retest confirmed the participant met exclusion criteria. The participant was never dosed. This randomisation criteria error was noted as a minor protocol deviation.

***CHMP comment***

Of the 11 participants enrolled in the study, 6 were assigned to Plegridy treatment.

Of the participants that withdrew treatment prematurely, the majority had been treated for period around 1.5 to 2 years. Hence, it appears that patient observation time for most withdrawers is relatively long.

***Recruitment***

Study 800MS301 was terminated early due to difficulty in recruitment and subsequent progress of the study. Despite numerous recruitment strategies and a recruitment period of 20 months, only 12 participants were recruited (1 participant who was a screen failure was mistakenly randomised before a laboratory retest confirmed the participant met exclusion criteria). After notification of all interested parties (investigators, institutional review boards, ethics committees, and regulatory agencies), Study 800MS301 was terminated by the Sponsor with the consent of the Food and Drug Administration.

***CHMP comment***

In the National Institutes of Health Clinical Trial Register, the Applicant indicated that the study was also terminated due to "changes in the paediatric MS landscape which no longer support placebo-controlled trials. Decision to stop study was not based on safety concerns" (ClinicalTrials.gov).

***Baseline data***

The mean (standard deviation [SD]) age overall was 15.6 (1.36) years, with the majority of participants in the 15 to 17 years category (9 of 11 participants, 82%). Baseline characteristics not related to the disease indication included Tanner developmental staging.

Overall, mean (SD) time since first MS symptoms prior to enrolment was 1.0 (1.26) years, and time since MS diagnosis was 0.6 (0.81) years. All but 1 participant had experienced an MS relapse prior to study start, with the majority of participants, 7 of 11 participants (64%), having experienced 1 relapse within the last year; relapses occurred a mean (standard deviation [SD]) 3.4 (6.27) months prior to study enrolment.

Most participants were treatment-naïve at the start of the study; 3 of 11 participants (27%) had received prior MS therapy [interferon ß-1a and methylprednisolone; Table 11, Abbreviated CS]. No participant had received disease-modifying therapies (DMTs).

***CHMP comment***

Participants had received their MS diagnosis a mean 7 months before study enrolment. Almost all participants had experienced an MS relapse prior to study entry, while only 3 participants reportedly had received prior MS therapy.

***Number analysed***

No comparisons between treatment groups were performed due to the very small sample size and early termination of the study.

***Efficacy results***

Drug efficacy and patient-reported outcome (PRO) data were not summarised.

***CHMP comment***

No summary of efficacy data or expert opinion was presented by the Applicant. The Applicant is requested to provide a descriptive summary of the available efficacy data (**OC**).

***Safety results***

All participants experienced at least 1 AE. Most participants had events of mild and moderate severity, and 1 participant (9.1%) in the Placebo group experienced 1 severe AE. Four of 11 participants (36.4%) had events that were considered related to study treatment. A total of 2 participants (18.2%) experienced SAEs; these SAEs were not considered related to study treatment. There were no fatal SAEs reported.

Adverse events that reported at least 10% higher incidence for active treatments compared to placebo included headache (54.5%) and abdominal pain (18.2%).

No AEs were reported as a result of abnormal laboratory (hematology, blood chemistry, urinalysis), vital signs, or ECG assessments.

At screening, 9 of 11 participants were positive for anti-PEG antibodies. Ten of 11 participants (91%) were positive for anti-PEG antibodies at the end of the study at Week 96.

As for binding and neutralising antibodies for Plegridy, a neutralising antibody test was conducted if a sample had anti-Plegridy antibodies. No participants were positive for neutralising anti-Plegridy antibodies at the end of the study at Week 96.

***CHMP comment***

The safety assessment in this study is limited and very general. The Applicant did not specify which events occurred during Plegridy treatment specifically. The events of feeling cold/chillness and injection site erythema and bruising, that were experienced by some participants, are listed as (very) common ADRs in the SmPC of Plegridy. Based on AE reporting, it can be agreed that no new safety concerns were identified from this study.

It is noted that 2 of 6 Plegridy-treated participants (33.3%) developed anti-Plegridy antibodies. These percentages are substantially higher than observed in the adult population with RRMS, but the transient nature of the neutralising antibodies (in 1 patient only) does not allow for any conclusions on safety or efficacy.

Furthermore, almost all study participants (81.8 %) had anti-PEG antibodies prior to the start of the study.

## 2.3.3. Discussion on clinical aspects

For this Article 46 procedure, the MAH submitted an abbreviated Clinical Study Report for the uncompleted paediatric Study 800MS301. This study was not part of the Applicant's PIP [1].

[1] One paediatric study, Study 105MS306, is included in the Applicant's PIP EMEA-001129-PIP01-11, and is currently ongoing. Study 105MS306 is an open-label, randomized, active-controlled study to evaluate safety and efficacy of pegylated human interferon ß-1a in children from 10 years to less than 18 years of age with RRMS. In a recent PIP modification (EMEA-001129-PIP01-11-M5), the Applicant has requested some changes to the design and timelines of this study, due to recruitment difficulties.

In general, Study 800MS301, as proposed, was a well-designed study of sufficient length to evaluate the efficacy and safety of Plegridy and Tecfidera in paediatric patients with RRMS. However, these objectives could not be met due to early study termination; only 4.2% of the anticipated 260 subjects were recruited. Explanations for the low recruitment are lacking. Since the study has been stopped, this is not further pursued. Note that in the National Institutes of Health Clinical Trial Register, the Applicant indicated that the study was also terminated due to "changes in the paediatric MS landscape which no longer support placebo-controlled trials. The decision to stop study was not based on safety concerns."

Relevant efficacy data, with a long patient observation time, are available for almost all participants. The Applicant has provided a descriptive summary of the available efficacy data for verification.

The safety assessment in this study is limited. The events of feeling cold/chillness and injection site erythema and bruising, that were experienced by some participants, are listed as (very) common ADRs in the SmPC of Plegridy. Other events reported in more than one patient or in one patient more than once (i.e., headache, chest pain, flu-like symptoms) are listed. Although immunogenicity appears higher in children than in adults, it also seems transient. Thus, the assessment of the safety data does not indicate important or new safety concerns.

# 3. Rapporteur's overall conclusion and recommendation

The Applicant did not assess the efficacy of Plegridy in children aged 10-17 years with RRMS due to early termination of the study. The limited safety data from 6 patients treated with Plegridy did not indicate new safety signals. On request, the Applicant has updated the abbreviated Clinical Study Report with efficacy data, and it is agreed that the SmPC of Plegridy does not need to be updated.

The submitted study results do not change the benefit-risk of Plegridy in adults with RRMS.

☒ **Fulfilled**