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SCIENCE MEDICINES HEALTH

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Human Medicines Division

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

TECFIDERA

dimethyl fumarate

Procedure no: EMEA/H/C/002601/P46/023

Note

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

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1. Introduction

This report covers the following post-authorisation commitments undertaken by the MAH:

Completed paediatric study, Study 800MS301

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 (Tecfidera®) and BIIB017 (Plegridy®) for the treatment of relapsing-remitting multiple sclerosis.

Given the small number of participants in the study, an abbreviated clinical overview-addendum has been provided that only includes the study synopsis of study 800MS301 without any critical expert evaluation.

No changes to the PI are proposed based on the results of study 800MS301.

2. Summary of data submitted

PAM – Article 46 – EMEA/H/C/002601/PAM/023 Submission of final Clinical Study Report for Study 800MS301– Initial Submission. Delivery due date 20 January 2023. Study 800MS301 is not listed in the RMP.

Study Number: 800MS301

Date of First Treatment: 16 April 2019

End of Study Date: 21 July 2022

Date of the final (abbreviated) Clinical Study Report: 15 December 2022

2.1. Methods

Study 800MS301 is a Phase 3b, 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.

Study sites

A total of 6 sites enrolled 11 participants.

Objectives

Primary Objective: To evaluate the efficacy of Tecfidera and Plegridy, both compared with placebo, in paediatric participants with RRMS

Secondary Objectives:

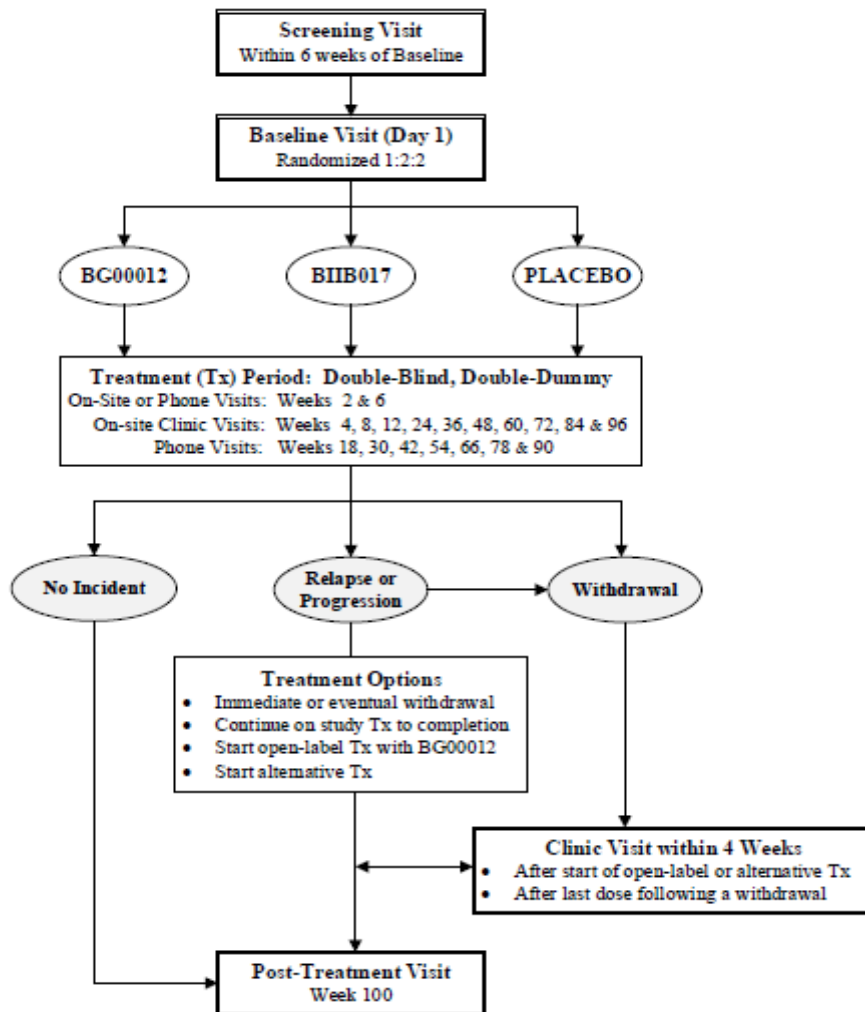
- To evaluate the safety and tolerability of Tecfidera and Plegridy
- To assess the effect of Tecfidera and Plegridy, both compared with placebo, on additional clinical and radiological measures of disease activity

Additional Objectives: To collect additional safety and efficacy information

The study design is presented in Figure 1.

Figure 1: Study design

Figure 1: Study Design



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.

Blinding

This study was a double-blinded, double-dummy, placebo-controlled trial. To maintain the blind all participants received a placebo for the treatment they were not assigned.

Study population

Main inclusion criteria

- Aged 10 to 17 years old, inclusive, at the time of informed consent. The minimum age could have been older than 10 years as required by country specific regulations and/or local ethics committees.
- Diagnosis of RRMS as defined by the revised consensus definition for paediatric multiple sclerosis (MS).
- Expanded Disability Status Scale (EDSS) score between 0.0 and 5.0.
- Body weight of ≥ 30 kg; the minimum weight for inclusion in the study could have been greater than 30 kg if required by country-specific regulations and/or local ethics committees.
- Experienced ≥ 1 relapse in the 12 months prior to randomization (Day 1), must have had evidence of asymptomatic disease activity (gadolinium [Gd]-positive lesions) seen on MRI in the 6 months prior to randomization (Day 1), or must have had ≥ 2 relapses in the 24 months prior to randomization (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.

Main exclusion criteria

- 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 had superimposed relapses but were distinguished from relapsing participants by the lack of clinically stable periods or clinical improvement.
- Disorders mimicking MS, such as other demyelinating disorders (e.g., acute disseminated encephalomyelitis), systemic autoimmune disorders, metabolic disorders, and infectious disorders.
- History of suicidal ideation within 3 months prior to randomization (Day 1) or an episode of severe depression within 3 months prior to randomization (Day 1). Severe depression was defined as an episode of depression that required hospitalization or was otherwise regarded as severe by the Investigator.
- Occurrence of an MS relapse within the 30 days prior to randomization (Day 1) and/or the participant had not stabilized from a previous relapse prior to randomization.
- Any previous treatment with Fumaderm®, Tecfidera, or Plegridy.
- Treatment with other agents to treat MS symptoms or underlying disease as specified below: Prior treatment with any therapeutic monoclonal antibody (e.g., rituximab, natalizumab, or alemtuzumab); prior treatment with any of the following within 12 months prior to randomization (Day 1): cyclophosphamide, mitoxantrone; prior treatment with any of the following within 12 months prior to randomization (Day 1): cyclophosphamide, mitoxantrone; prior treatment with any of the following within 6 months prior to randomization (Day 1): cyclosporine, fingolimod, plasma exchange or cytappheresis, intravenous immunoglobulin,

azathioprine, mycophenolate mofetil, methotrexate, teriflunomide, laquinimod; prior treatment with systemic corticosteroids, including agents that may have acted through the corticosteroid pathway (e.g., low-dose naltrexone) within 30 days prior to randomization (Day 1); prior treatment with glatiramer acetate, interferon (IFN), or 4-aminopyridine or related products (except subjects on a stable dose of controlled-release fampridine for at least 3 months) within 4 weeks prior to randomization (Day 1).

Duration of Treatment and Follow-Up:

The planned study duration for each participant was approximately 106 weeks: a 6-week Screening Period, a 96-week (2 year) Treatment Period, and a 4-week Post-Treatment Period. This was a single period study, with no follow-up period. Screening took place up to 6 weeks prior to Study Day 1.

Criteria for evaluation

Efficacy:

Primary Endpoint: Time to first relapse (TTFR)

Safety:

Secondary Endpoint:

- 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
 - Annualized relapse rate at Weeks 48 and 96
- Additional Endpoints

Additional Endpoints

- Changes from baseline in vital signs, electrocardiograms (ECGs), and clinical laboratory data
- Growth and development parameters, including height, weight, and Tanner stage
- Binding and neutralizing antibodies to IFN β -1a; binding antibodies to polyethylene glycol (PEG)
- Depression (monitored using the Children's Depression Rating Scale and the Columbia Suicide Severity Rating Scale)
- Symbol Digit Modalities Test (SDMT)
- Change from baseline in the volume of T2 hyperintense lesions; number of new or newly enlarging T1 hypointense lesions; brain atrophy
- Fatigue as measured by the Pediatric Quality of Life Inventory (PedsQL™) Multidimensional Fatigue questionnaire
- Quality of life as measured by the PedsQL questionnaire
- Proportion of participants with disability progression and time to disability progression

Sample Size

Approximately 260 participants, aged 10 to 17 years, inclusive, with a diagnosis of RRMS as defined by the revised consensus definition for pediatric MS [Krupp 2013; Polman 2011] were planned to be enrolled at approximately 50 sites globally.

2.2. Results and Applicant's conclusion on the results

Study population

At the time the study was terminated, a total of 11 participants had been randomised and dosed (2 participants in the Tecfidera 240 mg BID group, 6 participants in the Plegridy 125 µg SC Q2W 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.

Seven of 11 participants completed the study, and only 4 of 11 participants completed the study treatment. The study protocol, version 4, stated that participants with progressive disease who either discontinued study treatment and switched to an alternative therapy or open-label therapy or declined alternative treatment could continue to attend study visits as scheduled or withdraw, at their decision. Three participants, one under BG12 and 2 under placebo exercised this option and completed the study visits despite being switched to other therapies. Therefore, 7 of 11 participants completed the study, and 4 of 11 participants (one under BG12 and three under BIIB017) completed the study treatment. However, a total of 7 participants (including 3 participants who completed the study) discontinued study treatment early: 2 discontinued because the study was terminated by the Sponsor, 2 discontinued due to disease progression (one under BG12 and one under placebo), 1 under placebo withdrew due to an AE, 1 under BIIB017 withdrew because of concern of placebo and side effect of injection drug, and 1 under placebo discontinued treatment for other reasons (participant switched to open-label therapy).

Demographics and Baseline Disease Characteristics

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%). Most participants were female (8 of 11 participants, 73%) and White (10 of 11 participants, 91%).

Overall, mean (SD) time since first MS symptoms prior to enrollment 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 enrollment.

Most participants were treatment-naïve at the start of the study; 3 of 11 participants (27%) had received prior MS therapy. No participant received disease-modifying therapies (DMTs).

Efficacy - Results

Study 800MS301 was terminated early due to limited participant enrollment and subsequent progress of the study. As a result, the data collected were insufficient to support the original study objectives. Drug efficacy and PRO data were not summarised and only data listings were provided.

Safety - Results

The data collected in Study 800MS301 were insufficient to support the original study objectives.

All participants experienced at least 1 AE. Most participants had events of mild and moderate severity (5 of 11 participants, 45.5%, each), 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, 1 in the Tecfidera 240 mg BID group and 1 in the Placebo group; these SAEs were not considered related to study treatment. One participant in the Placebo group experienced an SAE of MS relapse that led to both study treatment discontinuation and withdrawal from the study. 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 neutralizing antibodies for Plegridy, a neutralizing antibody test was conducted if a sample had anti-Plegridy antibodies. Overall, 2 participants (18.2%) tested positive for anti-Plegridy antibodies during the study. However, only 1 participant (9.1%) tested positive for neutralizing anti-Plegridy antibodies. No participants were positive for neutralizing anti-Plegridy antibodies at the end of the study at Week 96.

Conclusions

At the time the study was terminated, a total of 11 participants had been enrolled. All participants were randomised and dosed (2 in the Tecfidera 240 mg BID group, 6 in the Plegridy 125 µg SC Q2W group, and 3 in the Placebo group).

With regard to efficacy, no comparisons between treatment groups were performed due to the very small sample size and early termination of the study.

All participants experienced at least 1 AE. Four of 11 participants (36.4%) had events that were considered related to study treatment. A total of 2 participants experienced SAEs, 1 SAE of MS relapse in the Tecfidera 240 mg BID group and 1 SAE of MS relapse in the placebo group; these SAEs were not considered related to study treatment. One participant in the Placebo group experienced an SAE of MS relapse that led to both study treatment discontinuation and withdrawal from the study. Adverse events that reported at least 10% higher incidence for active treatments compared to placebo included headache (54.5%) and abdominal pain (18.2%). There were no fatal SAEs reported.

No vital sign, laboratory, or ECG AEs were noted during the study.

The sample size was too small for any meaningful comparison between treatment groups. No new safety signals were identified from this study.

3. Scientific discussion

Study 800MS301 was terminated early due to difficulty in recruitment and subsequent progress of the study. Despite a recruitment period of 20 months only 12 participants were recruited for the study (1

participant who was a screen failure was mistakenly randomized before a laboratory retest confirmed the participant met exclusion criteria).

It is stated in the Clinical Study Report, that 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. Study 800MS301 is not listed in the RMP.

At the time the study was terminated, only 16 subjects had been screened and 11 participants were randomised and dosed, with only 2 subjects enrolled to the Tecfidera treatment arm.

As a result, the data collected were insufficient to support the original study objectives and the sample size was too small for any meaningful interpretation of efficacy results, especially with regard to comparison between treatment groups. No new safety signals were identified from this study.

4. Overall conclusion

Study 800MS301 was a randomised, double-blind, double-dummy, placebo-controlled study to evaluate the efficacy and safety of BG00012 (Tecfidera®) and BIIB017 (Plegridy®) for the treatment of RRMS in paediatric subjects.

Data with respect to efficacy are very limited, and no interpretation of these data is possible. There were no unexpected safety findings during this study. Based on very limited data, treatment with Tecfidera in study 800MS301 showed safety findings that can be considered to be in line with findings from Part 1 of study 109MS306 that led to the approval of Tecfidera in paediatric patients aged 13 years and over (please refer to EMEA/H/C/002601/II/0073).

Overall, the limited data do not affect the positive benefit/risk profile of Tecfidera in paediatric patients aged 13 years and over.

The PAM, concerning the submission of results of study 800MS301 is fulfilled since the final report, although abbreviated, has been provided.

☒ **PAM fulfilled**

No regulatory action required.