



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

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Human Medicines Evaluation 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/P46/020

### **Note**

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

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**Official address** Domenico Scarlattilaan 6 • 1083 HS Amsterdam • The Netherlands

**Address for visits and deliveries** Refer to [www.ema.europa.eu/how-to-find-us](http://www.ema.europa.eu/how-to-find-us)

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# 1. Introduction

On 22 March 2019, the MAH submitted a completed paediatric study for TECFIDERA (dimethyl fumarate), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the post-authorisation measure.

A clinical overview-addendum, only including the study synopsis of study 109MS311 without any critical expert evaluation has also been provided.

## 2. Scientific discussion

### 2.1. Information on the development program

The MAH stated that study "A Multicenter Extension Study to Determine the Long-Term Safety and Efficacy of BG00012 in Pediatric Subjects With Relapsing-Remitting Multiple Sclerosis" – 109MS311 is a stand-alone study.

Study 109MS311 is the extension of study 109MS202 that has been submitted via Type II variation in 2017, leading to changes/update of the SmPC.

Study 109S202 was a 24 week, open-label, multicentre, uncontrolled study to assess the effect of Tecfidera on brain magnetic resonance imaging (MRI) lesions (number of new or newly enlarging T2 hyperintense lesions), as well as to evaluate the pharmacokinetics, safety and tolerability in paediatric patients with relapsing-remitting multiple sclerosis from 10 to 17 years of age. Although efficacy results showed a trend towards reduction of new or newly enlarging T2 hyperintense lesions post-treatment vs. pre-treatment, the study design did not allow a firm conclusion on clinical efficacy in paediatrics as compared to adults with RRMS. No additional safety concerns related to BG00012 administration in paediatrics have been noted compared to adults based on the small number of subjects. The safety profile in paediatrics comprised data of 22 subjects with a median age of 16 years and a body weight in the range of 46 to 91.2 kg (mean 66.23 kg). It was hence concluded that these patients comply with the adult population but not necessarily with younger paediatrics. Moreover, the duration of the study did not allow concluding on the known safety issues of Tecfidera over time e.g. lymphocyte count decreases. In the adult studies, a 30% reduction in lymphocyte counts developed over the course of 48 weeks of treatment contrasting a 18% reduction over 24 weeks of treatment in paediatrics. Regarding the pharmacokinetic profile of Tecfidera it was concluded that the rate and extent of exposure in adolescent patients was comparable to adult subjects. Paediatric patients < 13 years of age have not been evaluated, therefore the conclusions relate to adolescents only.

For further information, reference is made to the final updated variation assessment report (EMA/H/C/002601/II/0042). Study 109MS202 as concerned in that variation procedure as well as study 109MS311 are not part of the Tecfidera PIP.

The applicant stated that a Type II variation will be submitted after the company`s conclusion of the internal review to update the SmPC further. In the meantime, this variation has already been submitted.

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

The BG00012 dosage selected for this study (240 mg BID) given as 2 capsules of 120 mg, is the approved BG00012 dosing regimen in adult patients with MS.

## **2.3. Clinical aspects**

### **2.3.1. Introduction**

Multiple sclerosis primarily affects adults, with clinical onset occurring most commonly between 20 and 40 years of age [O'Connor and Canadian Multiple Sclerosis Working Group 2002]. Approximately 2.2% to 4.4% of all MS cases have onset during adolescence or childhood [Chitnis 2011], with girls affected more than boys, and most cases being relapsing-remitting multiple sclerosis (RRMS).

The most commonly used first-line therapies for the treatment of MS in the paediatric population are interferons and glatiramer acetate [Waldman 2011]. Fingolimod is the only MS therapy currently approved by the European Medicines Agency (EMA) for use in pediatric MS patients aged 10 to 17 years old [Chitnis 2018].

The MAH submitted a final report for Study 109MS311 "A Multicenter Extension Study to Determine the Long-Term Safety and Efficacy of BG00012 in Pediatric Subjects With Relapsing-Remitting Multiple Sclerosis ". An update of the SmPC will be submitted via Type II variation after the company`s conclusion of the internal review.

However, it should be noticed that there is an ongoing randomised, open-label, controlled paediatric study (study 109MS306) which is agreed in the PIP (P/0167/2017). Upon completion of this study, the SmPC should be further updated.

### **2.3.2. Clinical study**

#### **Study 109MS311 "A Multicenter Extension Study to Determine the Long-Term Safety and Efficacy of BG00012 in Pediatric Subjects With Relapsing-Remitting Multiple Sclerosis"**

##### **Description**

##### **Methods**

##### **Objectives**

Primary Objective: to evaluate the long-term safety of BG00012 in participants who completed Study 109MS202.

Secondary Objectives: to evaluate the long-term efficacy of BG00012 and to describe the long-term multiple sclerosis (MS) outcomes in participants who completed Study 109MS202.

##### **Study design**

Study 109MS311, an open-label extension study, was designed to evaluate the long-term safety and efficacy of BG00012 in pediatric participants with relapsing-remitting multiple sclerosis (RRMS).

The number of participants who were eligible for this study was determined by the number of participants who had completed Study 109MS202 as per protocol.

Participants from Study 109MS202 who had completed all study assessments and remained on BG00012 treatment at 240 mg twice daily (BID) had the option to enrol in Study 109MS311 or to return for a Safety Follow-Up Visit 4 weeks after the last dose of study treatment. This study consisted of a 4-week enrollment period (if the Final Study Visit from Study 109MS202 could not have been combined with the Baseline Visit for this study), and eligible participants from Study 109MS202 were enrolled to Study 109MS311. At the end of the Baseline Period, starting at Day 1, participants received BG00012 240 mg BID (2 capsules of 120 mg) orally for 96 weeks, and a Safety Follow-Up Visit was conducted up to 4 weeks after the last dose of study treatment.

Safety and efficacy were assessed throughout the study. Participants who withdrew prematurely from the study completed the Early Withdrawal Visit, which was conducted as soon as possible and no later than 4 weeks after the participant's last dose of study treatment. Participants who withdrew prematurely were encouraged to complete the Safety Follow-Up Visit 4 weeks after the last dose of study treatment.

### ***Study population /Sample size***

The sample size for this extension study was determined by the number of eligible participants who completed Study 109MS202. Twenty participants (all of the patients who completed study 109MS202) enrolled in Study 109MS311 and were analysed.

### ***Treatments***

All participants received BG00012 240 mg BID (2 capsules of 120 mg) orally for up to 96 weeks.

### ***Outcomes/endpoints***

Primary objective: to evaluate the long-term safety of BG00012 in participants who completed Study 109MS202.

Secondary objectives: to evaluate the long-term efficacy of BG00012 and to describe the long-term MS outcomes in participants who completed Study 109MS202.

The primary endpoint was the incidence of adverse events (AEs), serious AEs (SAEs), and discontinuations of study treatment due to an AE.

Secondary Endpoints:

- the total number of new or newly enlarging T2 hyperintense lesions on brain magnetic resonance imaging (MRI) scans, the annualized relapse rate (ARR), and the proportion of participants who experienced 1 or more relapses during the study period.
- the degree of disability as measured by the Expanded Disability Status Scale (EDSS) and disability progression (as measured by at least a 1.0-point increase on the EDSS from baseline EDSS  $\geq 1.0$  that is sustained for 24 weeks, or at least a 1.5-point increase on the EDSS from baseline EDSS = 0 that is sustained for 24 weeks).

Pharmacokinetics and pharmacodynamics were not analysed in this study.

### ***Statistical Methods***

As this study contained a single treatment group, descriptive statistics was the primary approach to analyze the data.

Baseline data were defined as data collected prior to the administration of BG00012 on Day 1 of Study 109MS311, which should have been the final visit in Study 109MS202. If the final visit in Study 109MS202 could not have been used as Baseline, Day 1 of Study 109MS311 was considered Baseline.

Lymphocyte count data were summarized by time-points on study treatment. Additionally, lymphocyte count over time post-treatment and the time to recovery were descriptively summarized for participants who developed a decrease in lymphocyte count (<lower limit of normal).

## **Results**

### ***Recruitment/ Number analysed***

A total of 20 participants who completed Study 109MS202 were enrolled at 12 sites in 10 countries. The date of the first participant's first treatment was 22 February 2016. The last participant completed the study on 24 September 2018.

Seventeen (85%) participants completed the study. Three (15%) participants discontinued study treatment and withdrew from the study due to Investigator decision (2 [10%] participants) or participant decision (classified as "other;" 1 [5%] participant) following the detection of new lesions on MRI.

The analysis population for the primary endpoint was defined as all participants who received at least 1 dose of BG00012 in this study and included all 20 participants. The population for the analysis of efficacy endpoints included all participants who received at least 1 dose of BG00012 in this study and who had an evaluation of the efficacy endpoints under analysis. No participants were excluded from analyses of the efficacy endpoints.

### ***Baseline data***

The median age of participants was 17.0 years old (range: 14 to 18 years old), and most participants were female (13 [65%] participants).

Baseline disease characteristics were collected at the Study 109MS202 Screening Visit and were not reassessed prior to enrollment into Study 109MS311. Based on the date of enrollment into Study 109MS202, the median time since the first MS symptom occurred was 2.0 years (range: 1 to 9 years), and the median time since the first MS diagnosis was 1.0 year (range: 1 to 7 years). The median number of relapses in the 12 months prior to Screening for Study 109MS202 was 1.0 (range: 0 to 4 relapses) and was 2.0 (range: 0 to 5 relapses) each in the 2 and 3 years prior to Screening for Study 109MS202. The median time since the last relapse to the start of BG00012 administration in Study 109MS202 was 48.5 weeks (range: 38 to 104 weeks). The median time since the last relapse was not recalculated at the time of participant enrolment into Study 109MS311. Two (10%) participants had no relapses in the 12 months prior to the Study 109MS202 Screening Visit.

### ***Efficacy results***

Of the 17 participants with an MRI evaluation at Week 16 and Week 24, 12 (71%) participants had no new or newly enlarged T2 lesions from Week 16 to Week 24. Of the 10 participants with MRI evaluation at Week 64 and Week 72, 8 (80%) participants had no new or newly enlarged T2 lesions from Week 64 to Week 72.

The total number of relapses in the 20 participants who continued from Study 109MS202 into Study 109MS311 decreased from 29 relapses at 1 year prior to enrolment into Study 109MS202 to 6 relapses during the 24-week period evaluated during Study 109MS202, and decreased even further to 4

relapses during the 96 weeks evaluated in Study 109MS311, for a total of 10 relapses over 120 weeks on treatment. The number of participants with no relapses increased from 2 participants at 1 year prior to enrolment into Study 109MS202 to 13 participants over 120 weeks on treatment.

The unadjusted ARR for the 1-year period prior to Study 109MS202 study entry was 1.5 relapses and for the 24-week treatment period in Study 109MS202 was 0.6 relapses. The unadjusted ARR continued to decrease to 0.1 relapses over the 96 weeks analysed in Study 109MS311.

Two (10%) participants experienced a protocol-defined relapse (new or recurrent neurological symptoms not associated with fever or infection, lasting at least 24 hours, and accompanied by new objective neurological findings upon examination).

Three participants met the protocol definition of disability progression during the study period, of which 2 participants had an associated event of MS relapse. The median EDSS score was 1.00 (range: 0.0 to between 2.5 and 3.5) at each time-point evaluated, except at Week 72, when the median EDSS score was 1.25 (range: 0.0 to 3.5).

### **Safety results**

The median time on treatment was 669.0 days (range: 222 to 697 days), and the median total dose received was 320,040.0 mg (range: 106,080 to 331,920 mg).

Consistent with the safety profile seen in Study 109MS202, no new safety concerns related to treatment with long-term BG00012 were identified in this study of pediatric participants with MS.

The most common AEs among participants were flushing (5 [25%] participants), MS relapse (4 [20%] participants), and headache, abdominal pain, upper respiratory tract infection, viral upper respiratory tract infection, cough, and dysmenorrhea (3 [15%] participants each).

The majority of AEs reported in this study were mild or moderate in severity and were considered not related to study treatment.

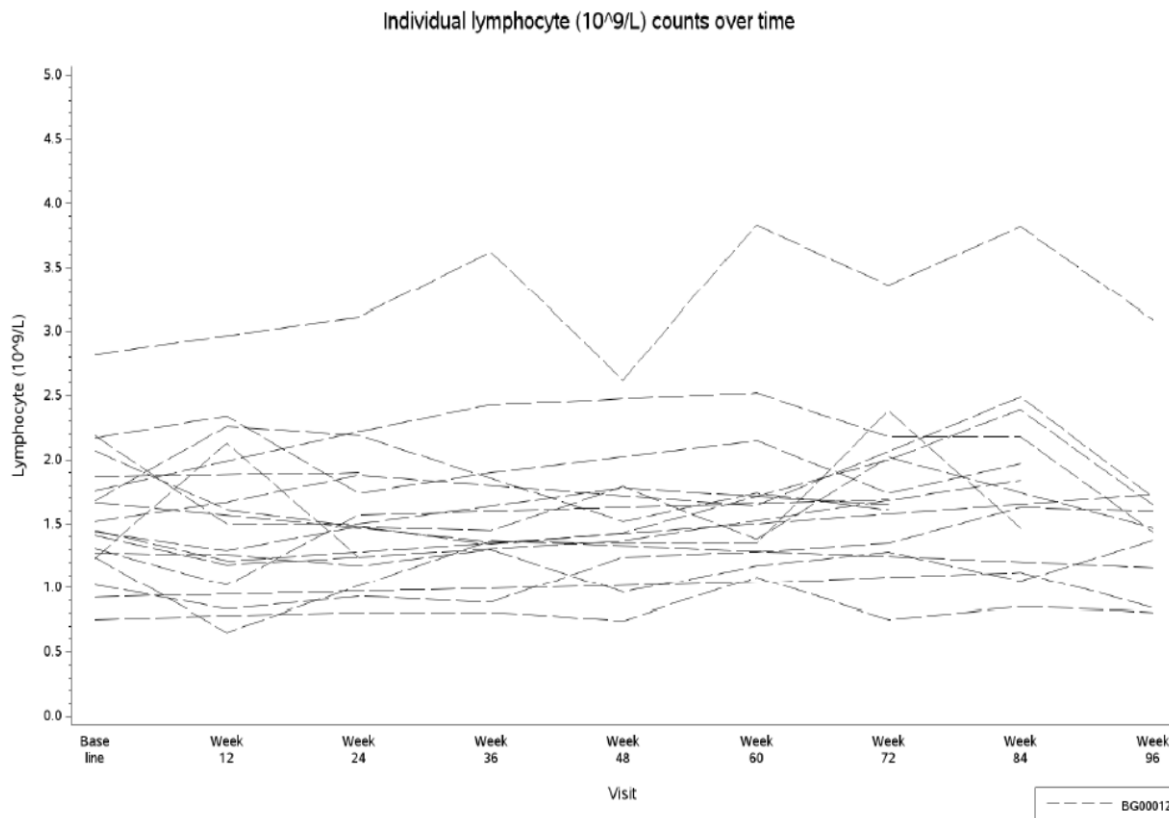
Three participants experienced 4 SAEs during the study, including 3 events of MS relapse and 1 event of abdominal pain that required hospitalization.

No participants died during the study, discontinued from study treatment due to an AE, or withdrew from the study due to an AE.

No apparent treatment-related or dose-related trends were observed in clinical laboratory parameters, vital signs, or ECGs. Results of laboratory, vital sign, and ECG assessments did not reveal any new safety concerns.

Lymphocyte counts generally remained stable throughout study treatment, and low lymphocyte counts were not associated with any related AEs such as infection or fever. However, 4 out of the 20 patients had no lymphocyte count at week 96 limiting the overall interpretation.

Figure 1



Shifts from normal, high, and unknown at baseline to low lymphocyte values were reported in 4 (22%) participants and a shift from normal, low, and unknown at baseline to high in 1 (5%) participant. No participants had lymphocyte counts  $\leq 0.5 \times 10^9/L$  during the study period. Three participants had a lymphocyte count  $< 0.8 \times 10^9/L$  during the study period; 1 participant had a lymphocyte count of  $0.68 \times 10^9/L$  at an unscheduled visit after the end of treatment visit; and 1 participant had a lymphocyte count of  $0.75 \times 10^9/L$  at baseline. This participant's lymphocyte counts fluctuated between  $0.55 \times 10^9/L$  and  $1.17 \times 10^9/L$  through the last follow-up visit 147 days after the end of study visit. A third participant had a lymphocyte count of  $0.65 \times 10^9/L$  at the Week 12 visit. Overall, the mean lymphocyte counts during treatment with BG00012 fluctuated throughout the study period, from  $1.587 \times 10^9/L$  at baseline to  $1.458 \times 10^9/L$  at Week 12, then increased to  $1.892 \times 10^9/L$  at Week 84, and decreased to  $1.534 \times 10^9/L$  at Week 96.

### 2.3.3. Discussion on clinical aspects

No new safety concerns were identified in this long-term extension study of paediatric participants with RRMS treated with Tecfidera, and the findings seem to be consistent with the safety profile seen in the initial paediatric study, Study 109MS202 and in the adult population. However, caution should be taken in interpreting these results due to the low number of participants (20 patients). In addition, 4 patients did not provide lymphocyte counts at the end of the study, week 96.

Although the efficacy results of the submitted open-label extension study, study 109MS311, suggest maintenance of effect of BG00012 on new or newly enlarged T2 hyperintense lesions and on relapses and the unadjusted ARR over 96 weeks of treatment, the study design (open-label, single-arm, small sample size) does not allow a firm conclusion on clinical efficacy in paediatric RRMS patients. On account of selection bias, open label extension studies should generally be interpreted with caution.



### 3. CHMP overall conclusion and recommendation

The submitted study 109MS311 does not change the known benefit-risk profile of TECFIDERA (dimethyl fumarate) in the treatment of RRMS. No proposals for SmPC and PL changes were submitted by the applicant within this procedure. However, in the meantime a Type II variation, that is not part of this assessment, has been submitted to update the SmPC further (TECFIDERA EMEA/H/C/002601/II/0059).

**Fulfilled:**

No regulatory action required.