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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tecfidera

Common Name: dimethyl fumarate

Procedure No. EMEA/H/C/002601/0000/Rev 1

Note

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

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List of abbreviations

9HPT	Nine-Hole Peg Test
AE	Adverse Event
AGIS	Acute Gastrointestinal Symptom Scale
AKr1b8	Aldo-Keto Reductase Family 1 Member B8
ALT	Alanine transaminase/Alanine Aminotransferase
ANOVA	Analysis of Variance
ARR	Annualised Relapse Rate
ASA	Acetylsalicylic Acid
AST	Aspartate transaminase/Aspartate Aminotransferase
ATP	Adenosine Triphosphate
AUC	Area Under Curve
B2M	Beta-2 Microglobulin
BCS	Biopharmaceutics Classification System
BID	Twice Daily
BUN	Blood Urea Nitrogen
CEP	Certificate of Suitability of the European Pharmacopeia
CHMP	Committee For Medicinal Products for Human Use
CI	Confidence Interval
Cl/F	Apparent Clearance
Cmax	Peak Plasma Concentration
CNS	Central Nervous System
CREA	Creatinine
CV	Cardiovascular
CYPs	Cytochromes
DMF	Dimethyl Fumarate
DMFAE	Dimethylfumaric ester
DMT	Disease Modifying Therapy
DSC	Differential Scanning Calorimetry
EAE	Experimental Autoimmune Encephalomyelitis
ECG	Electrocardiogram
EDSS	Expanded Disability Status Scale
EE	Efficacy Evaluable
eGFR	Estimated Glomerular Filtration Rate

EQ-5D	European Quality of Life-5 Dimensions Health Survey
ERA	Environmental Risk Assessment
ESRD	End Stage Renal Disease
FA	Fumaric Acid
FACT	Fumaric acid compound therapy
FT-IR	Fourier Transform Infra-Red Spectroscopy
GA	Glatiramer acetate
GC	Gas Chromatography
Gclc	Glutamate –cysteine ligase catalytic subunit
GCP	Good Clinical Practices
Gd	Gadolinium
GFSS	Global Flushing Severity Scale
GGT	Gamma Glutamyl Transferase
GI	Gastrointestinal
GLP	Good Laboratory Practices
GSH	Gluthatione
h	Hour(s)
HbsAg	Hepatitis B Surface Antigen
HDPE	High Density Polyethylene
HIV	human immunodeficiency virus
HO-1	Heme Oxygenase-1
HPLC	High Performance Liquid Chromatography
HPMC	Hydroxypropyl-methylcellulose
HR	Hazard Ratio
i.m	Intramuscular
i.p	Intraperitoneal
i.v. or IV	Intravenous
ICH	International Conference on Harmonisation
ILN	Lymph node
INEC	Independent Neurology Evaluation Committee
IR	Infra-Red Spectroscopy
ITT	Intention To Treat
IVRS	centralised interactive voice response system
Kim-1	Kidney Injury Molecule 1
LC/MS	Liquid Chromatography/Mass Spectrometry

LD50	Median Lethal Dose
LDPE	Low Density Polyethylene
LFT	Liver Function Test
LLN	Lower Limit of Normal
MAH	Marketing Authorisation Holder
MEF	Monoethyl fumarate
MEFAE	Monoethylfumaric ester
MI	Myocardial Infarction
MLN	Mesenteric lymph node
MMF	Monomethyl Fumarate
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MS	Mass Spectrometry (in Quality part)
MSFC	Multiple Sclerosis Functional Composite
MTD	Maximum dose tolerated
MTR	Magnetization Transfer Ratio
NA	Not Applicable
NABT	normal appearing brain tissue
NADPH	Nicotinamide Adenine Dinucleotide Phosphate, Reduce form
NAS	New Active Substance Status
NMR	Nuclear Magnetic Resonance
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
NQ01	NAD(P)H dehydrogenase (quinone 1)
NrF2	Nuclear factor(erythroid-derived 2)-like 2
OGISS	Overall Gastrointestinal Symptom Scale
Osgin 1	Oxidative stress-induced growth inhibitor 1
PASAT3	3- Second Paced Auditroy Serial Addition Test
PBT	Persistent, Bioaccumulative, Toxic
PGD2	Prostaglandin D2
PGE2	Prostanglandin E2
PGF2α	Prostanglandin 2 alpha
P-gp	P-glycoprotein
Ph.Eur.	European Pharmacopeia
PIP	Paediatric Investigation Plan

PK	Pharmacokinetics
PML	Progressive Multifocal Leukoencephalopathy
PNM	Potentially Nephrotoxic Medication
PP	Per Protocol
PPMS	Primary Progressive Multiple Sclerosis
PRAC	Pharmacovigilance Risk Assessment Committee
PTH	Parathyroid Hormone
QD	Once Daily
QT	Interval between the start of the Q wave and the end of the T wave in the heart's electrical cycle
QTc	Corrected QT interval
RA	Rhumatoid Arthritis
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Relapsing Mutliple Sclerosis
RRMS	Relapsing Remitting Multiple Sclerosis
s.c	Subcutaneous
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SD	Standard Deviation
SF-36	Short Form 36 Heatlh Survey
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum Glutamic Pyruvate Transaminase
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SPMS	Secondary Progressive Multiple Sclerosis
Srxn 1	Thioredoxin reductase 1
t1/2	Half Life
T25FW	Time 25-Foot Walk
TCA	Tricarboxylic Acid
TGA	Thermogravimetric Analysis
TID	Three Times Daily
Tmax	Time to Peak Plasma Concentration
TNFα	Tumor Necrosis Factor-alpha
Trxnd1	Sulfiredoxin 1
TSE	Transmissible Spongiform Encephalopathy

ULN	Upper Limit of Normal
UV/VIS	Ultra-Violet/Visible Spectroscopy
VAS	Visual Analogue Scale
VFT	Visual Function Test
vs	Versus
WBC	White Blood Cells
WT	Wild Type
XRD	X-Ray Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Biogen Idec Ltd submitted on 28 February 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Tecfidera, through the centralised procedure under Article 3 (2)(b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21 July 2011. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of significant therapeutic innovation.

The applicant applied for the following indication:

disease modifying therapy in adult patients with relapsing multiple sclerosis to reduce the frequency of relapses and to delay the progression of disability.

The legal basis for this application refers to:

Article 8(3) of Directive No 2001/83/EC

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/76/2011 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

A new application was filed in the following countries: USA, Switzerland.

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturer responsible for batch release

Biogen Idec Denmark Manufacturing ApS
Biogen Idec Allé 1
DK-3400 Hillerod
Denmark

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Martina Weise

Co-Rapporteur: Robert James Hemmings

- The application was received by the EMA on 28 February 2012.
- The procedure started on 21 March 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 8 June 2012. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 8 June 2012.
- During the meeting on 19 July 2012, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 20 July 2013.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 11 October 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 23 November 2012.
- During the CHMP meeting on 13 December 2012, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 21 January 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 4 February 2013.
- During the PRAC meeting on 7 February 2013, the PRAC agreed on RMP Advice and Assessment Overview.
- During a meeting of a SAG on 13 February 2013, experts were convened to address questions raised by the CHMP.
- During the CHMP meeting on 21 February 2013, the CHMP agreed on a second list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the second CHMP List of Outstanding Issues on 27 February 2013.
- During the PRAC meeting on 7 March 2013, the PRAC agreed on RMP Advice and Assessment Overview.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the

second List of Outstanding Issues to all CHMP members on 11 March 2013.

- During the meeting on 21 March 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Tecfidera.
- By a letter dated 18 September 2013, the European Commission (EC) requested the CHMP to assess if dimethyl fumarate is different from Fumaderm composed of dimethyl fumarate, calcium salt of ethyl fumarate, magnesium salt of ethyl hydrogen fumarate and zinc salt of ethyl hydrogen fumarate with a view to include an assessment of the new active substance ('NAS') status of dimethyl fumarate in Tecfidera, as per applicant request.
- The applicant's request for NAS status was received by the EMA on 23 September 2013.
- The Rapporteur's Assessment Report on NAS status was circulated to all CHMP members on 9 October 2013.
- The Co-Rapporteur's Assessment Report on NAS status was circulated to all CHMP members on 9 October 2013.
- The Rapporteurs circulated the Joint Assessment Report to all CHMP members on 18 October 2013.
- During the CHMP meeting on 24 October 2013, the CHMP agreed on the consolidated List of Questions on NAS status to be sent to the applicant. The final consolidated List of Questions on NAS status was sent to the applicant on 24 October 2013.
- The applicant submitted the responses to the CHMP List of Questions on NAS status on 4 November 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 11 November 2013.
- During the meeting on 21 November 2013, the CHMP, in the light of the request from the EC, the overall data available and the scientific discussion within the Committee revised its initial opinion and considered that dimethyl fumarate is different from Fumaderm composed of dimethyl fumarate, calcium salt of ethyl fumarate, magnesium salt of ethyl hydrogen fumarate and zinc salt of ethyl hydrogen fumarate. Based on the review of the scientific evidence, and in line with clarification provided by the European Commission that:

i) a new active substance under Directive 2001/83/EC is a chemical substance not previously authorised as a medicinal product in the European Union (Annex I to the Notice to applicants Volume 2A, Procedures for marketing authorisation, Chapter 1, Marketing authorisations, June 2013) and,

ii) dimethyl fumarate is part of the medicinal product Fumaderm authorised in 1994 in Germany, but it has not been previously authorised as a medicinal product in the European Union,

the active substance of Tecfidera, dimethyl fumarate, is a new active substance.

- This assessment report was adopted by written procedure on 26 November 2013.

2. Scientific discussion

2.1. Introduction

Dimethyl fumarate[1] (DMF) is the dimethyl ester of fumaric acid. Both DMF and its primary metabolite monomethyl fumarate (MMF) were found to activate the *"Nuclear factor (erythroid-derived 2) like 2"* (Nrf2) transcriptional pathway which is the principle cellular defence system for responding to a variety of potentially toxic stimuli, including inflammatory and oxidative stress. By activating the Nrf2 pathway, DMF is claimed to reduce inflammatory responses in both peripheral and central cells, and promotes cytoprotection of central nervous system cells against toxic stressors, demonstrating beneficial effects on pathways known to exacerbate multiple sclerosis pathology.

The following indication was initially applied for: disease modifying therapy in adult patients with relapsing multiple sclerosis to reduce the frequency of relapses and to delay the progression of disability. The proposed posology was a starting dose of 120 mg twice a day. After 7 days, the dose is increased to the recommended dose of 240 mg twice a day.

The final recommended indication was: treatment of adult patients with relapsing remitting multiple sclerosis.

Multiple sclerosis (MS) is a chronic, progressive, autoimmune, debilitating neurodegenerative disorder with multifocal demyelination affecting the brain, optic nerves, and spinal cord and this process leads to neurological impairment and severe disability. It is one of the most common neurological diseases in young adults and the leading cause of non-traumatic disability in young and middle-aged adults. Typically, it begins in the second or third decade of life. In 2008, the global incidence was estimated at 2.5 individuals per 100 000 and the global prevalence was estimated at 30 individuals per 100 000, with women being at a two times higher likelihood to develop MS than men. Regionally, the estimated median prevalence of MS is greatest in Europe (80 per 100 000), followed by the Eastern Mediterranean (14.9 per 100 000), the Americas (8.3 per 100 000), the Western Pacific (5 per 100 000), Southeast Asia (2.8 per 100 000), and Africa (0.3 per 100 000).

The classification of MS into 4 distinct clinical categories was suggested by Lublin and Reingold shortly after the availability of the first disease-modifying treatments as a means to aid physicians in providing care. The following categories were included: relapsing-remitting (RR) MS, with clearly defined disease relapses (clinical attacks) with full recovery or with sequelae and residual deficit upon recovery, and with periods between relapses characterized by a lack of disease progression; secondary–progressive (SP) MS, with continuous neurological decline with or without superimposed relapses, that follows an initial period of RR disease; Primary–progressive (PP) MS, characterized by a slow worsening from onset, without superimposed relapses; and progressive–relapsing (PR) MS, indicating slow worsening from the onset, but with superimposed relapse events as well.

Relapsing forms of MS are the most frequent clinical presentation of the disease. Eighty-two (82) to 85 % of all patients present with relapsing-remitting (RR) MS, which is characterised by unpredictable acute episodes of neurological dysfunction named relapses, followed by variable recovery and periods of clinical stability. Within ten years more than 50% of patients who presented with a RR form eventually develop sustained deterioration with or without superimposed relapses; this form is called the secondary progressive variety of MS (SPMS).

[1] Also called BG00012 through the report

The term relapsing MS (RMS) applies to those patients either with a RRMS form or a SPMS form that are suffering relapses. Patients with RMS, in spite of suffering from different MS forms, constitute a common target for current treatments.

Currently, most of the available disease modifying therapies for MS are administered subcutaneously, intramuscularly or intravenously. These therapies aim to prevent relapses and ultimately to diminish the accumulation of disability. Due to their safety profiles (e.g. risk of opportunistic infections and secondary malignancies), most of the recently authorised products were considered as second line options.

2.2. Quality aspects

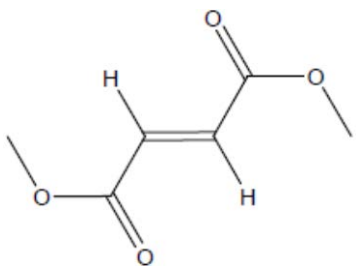
2.2.1. Introduction

The finished product is presented as gastro-resistant hard capsule containing 120 mg and 240 mg of dimethyl fumarate as active substance. The composition is described in section 6.1. of the SmPC.

The product is available in PVC/PE/PVDC-PVC/Alu blisters as described in section 6.5 of the SmPC.

2.2.2. Active substance

Dimethyl fumarate is a white to off-white powder, non-hygroscopic, BCS class 1 (highly soluble and highly permeable). The chemical name is Dimethyl (E)-butenedioate and has the following structural formula:



The molecular structure of the dimethyl fumarate has been confirmed by ^{1}H-NMR-, ^{13}C-NMR-, UV/VIS- spectroscopy, MS, FT-IR-spectrometry and X-ray powder diffraction. Typical spectra have been provided along with a detailed interpretation of signals. Only one crystal form has been observed by powder XRD and DSC investigations. Results of DSC/TGA thermograms confirm the affinity to sublimation.

Dimethyl fumarate has a non-chiral molecular structure. Polymorphism has not been observed for dimethyl fumarate.

Manufacture

The active substance is manufactured by two manufacturers. It is synthesized in two main steps using commercially available, well defined starting materials.

Dimethyl fumarate is synthesized by acid-catalysed esterification reaction (Fischer esterification). The manufacturing process of both manufacturers is the same except production scale batch sizes.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Specification

The active substance specification includes tests for appearance, identity (FT-IR, HPLC), assay (HPLC), impurities (HPLC), sulphate (Ph.Eur.), residual solvents (GC), heavy metals (Ph.Eur.), residue on ignition (Ph.Eur.) and particle size (laser diffraction).

Each specification parameter was sufficiently justified. Acceptance criteria for non-compendial tests have been set in accordance with batch results and CHMP/ICH guidelines.

Batch analysis data are provided for 36 production scale batches produced with the proposed synthetic route, from both manufacturing sites, and the batch analysis data show that the active ingredient can be manufactured reproducibly. The results are within the specifications and consistent from batch to batch.

Sufficient information is provided on potential impurities and residual solvents. Levels of impurities found in the batches of the active substance are low and well below specification limits.

Analytical procedures have been adequately described and appropriately validated.

Stability

Total number of 11 batches of the active substance from both manufacturing sites were put on stability testing as per ICH conditions: under long term (25°C/60%RH) and intermediate (30°C/65%RH) conditions for up to 60 months, and accelerated (40°C/75%RH) for up to 6 months.

The following parameters were tested: description, assay and impurities. Particle size does not change during storage, as confirmed by a suitable study; therefore, it is not necessary for it to be tested routinely in stability studies.

Photostability testing and forced degradation studies were conducted during the development. The results provide good information on degradation patterns of the active substance.

The stability results presented are well within specification. Re-test period of 60 months without special storage condition is considered justified.

2.2.3 Finished Medicinal Product

Pharmaceutical Development

The formulation development has been adequately described. The aim was to develop a delayed-release formulation that prevents release of the active ingredient in the gastric environment while allowing for rapid release of the active ingredient in the intestine region. Design of the finished product formulation was based on the desired gastro-resistant properties and on the physico-chemical properties of the active substance, which is highly soluble, independent of pH, and has high permeability. No physicochemical characteristics of the active substance were identified as critical.

The finished product is developed as 2 mm enteric-coated microtablets in size 0 hard gelatin capsules, in strengths 120 mg and 240 mg, respectively. The 120 mg strength capsules have white

body with green cap, for the 240 mg strength capsules with green body and green cap are used. The capsules are imprinted with company identifiers. The microtablets are composed of immediate release tablet core (dimethyl fumarate, crosscarmellose sodium as disintegrant, microcrystalline cellulose as diluent and binder, magnesium stearate as lubricant and talc (for 120 mg strength only) and colloidal anhydrous silica as glidants), and two layers of coating. All excipients used are compendial.

The 120 mg strength product was first developed and was used in the earlier phases of clinical development. The 240 mg strength capsule was developed subsequently based on the formulation for the 120 mg finished product. The composition of the microtablet cores slightly differs between the strengths. A bioequivalence study between the 120 mg and the 240 mg capsules shows bioequivalence between the two strengths in fasted state. The difference in excipients amounts has no impact on release and dissolution behaviour of the product. Both product strengths showed no significant release in 0.1 N HCl after 120 minutes (acid stage). In the buffer stage, percent dissolution was determined at the 10, 20, 30, 45, and 60 minute time points and a rapid release was observed for both product strengths.

Adventitious agents

Gelatine obtained from bovine/limed bone is used in the product. Valid TSE CEPs from the suppliers of gelatine used in the capsule manufacture are provided.

Magnesium stearate is of vegetable origin.

Manufacture of the product

During the manufacturing process, the excipients and active substance are blended together and compressed into microtablets. The microtablets are then coated and finally encapsulated into hard gelatin capsules. The capsules are packaged in PVC/PE/PVDC-PVC/Alu blisters. The material of the packaging complies with the Ph.Eur. requirements.

Critical quality attributes of the dosage form include friability, assay, content uniformity and disintegration in acid solution. All process steps related to these attributes are monitored by appropriate in-process controls. However, none of the manufacturing steps is considered critical. There are no intermediates in the manufacturing process of the product.

The manufacturing process was successfully validated on all product manufacturing steps, for three commercial scale batches per strength. All acceptance criteria have been met during validation, providing a high degree of assurance that the process will consistently produce material meeting its pre-determined specifications and quality attributes.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form. The product is tested for description of the capsule, description of the capsule content, identification (HPLC, UV), assay and impurities (HPLC), residual solvent isopropylalcohol (GC), uniformity of dosage units (Ph.Eur.), dissolution (Ph.Eur. – acid and buffer stage) and water content (Karl Fischer). The active substance is a known inhibitor of mould and bacteria growth. This was confirmed by a number of tests during the product development. Therefore, it is

acceptable to test microbial purity in the specification of the product only at first 10 commercial batches and then introduce skip testing, if microbial growth is not observed.

The acceptance criteria for all specification parameters are justified by batch results and comply with CHMP/ICH guidelines. Two impurities/degradation products are specified in the finished product. One of them is an endogenous substance in human body, the other is a metabolite; therefore, there are no safety concerns related to these impurities. All other impurities are controlled under the unspecified impurity limit.

All test methods for the finished product control are sufficiently described and appropriately validated.

Batch analysis results for 10 batches (120 mg) + 6 batches (240 mg) of commercial scale confirm consistency and uniformity of manufacture and indicate that the process is under control.

Stability of the product

Stability data of three full scale registration batches and three full scale validation batches stored under long term conditions at 25ºC/60%RH and intermediate conditions at 30ºC/65%RH for up to 60 months and for 6 months under accelerated conditions at 40ºC/75%RH were provided for the 120 mg strength. For the 240mg strength up to 12 months data was presented at the 30ºC/65%RH condition and up to 6 months under the same accelerated conditions. Results for 4 supportive clinical batches were also provided for the 120 mg strength. The studies were conducted according to appropriate CHMP/ICH guidelines. The stability batches are packed in the primary packaging proposed for marketing.

Bulk stability testing on capsules was conducted to establish a hold time prior to packaging. Ongoing studies to extend the hold time are being conducted in accordance with ICH Guideline Q1A Stability Testing of New Drug Substances and Products. The proposed 18 month hold time for drug product packaged in bulk and stored at or below 25°C is supported by 18 months of real time stability data.

Stability samples were tested for description of the capsule, description of the capsule content, assay, impurities, disintegration, dissolution and microbial purity. The analytical procedures used are stability indicating.

In addition, the product was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The product is not sensitive to light, if stored in the primary packaging. Additional temperature cycling studies were conducted to support transient exposure of the finished product at worst case distribution temperatures ranging from -20°C to 50°C. Results confirm the product stability at short term temperature excursions.

Based on available stability data, the proposed shelf-life and storage conditions as stated in the SmPC are acceptable.

2.2.3. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.2.4. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.5. Recommendation(s) for future quality development

N/A

2.3. Non-clinical aspects

All pivotal non-clinical safety pharmacology and toxicology studies were conducted in compliance with GLP regulations, except the *in vivo* cardiovascular and respiratory safety pharmacology study in dogs. Nonetheless, this *in vivo* safety pharmacology study in dogs has been adequately documented as study report and its results coincide with those of other investigations. Hence, the lack of formal GLP compliance is regarded as acceptable by the CHMP.

2.3.1. Introduction

Dimethyl fumarate (DMF/BG0012) has been evaluated in a series of in vitro and in vivo pharmacological tests used to characterise its effects on Nrf2 antioxidant pathway, inflammatory and neural cells.

2.3.2. Pharmacology

2.3.2.1. Primary pharmacodynamic studies

DMF is claimed to act as an anti-inflammatory and neuroprotective agent by activating the Nrf2 antioxidant pathway.

In vitro studies using immortalised adenocarcinoma or transformed human embryonic kidney cells, astrocytes, oligodendrocytes and hippocampal neurons revealed that DMF and its primary active metabolite MMF were both able to release the transcription factor Nrf2 from cytoplasmic repression and proteosomal degradation by direct alkylation of the Nrf2 repressor Keap 1 (Kelch-like erythroid cell-derived protein with CNC homology-associated protein 1). This resulted in increasing Nrf2 levels and thus activating downstream genes of the Nrf2 antioxidant pathway, i.e. NADPH dehydrogenase (NQO1) glutathione reductase and aldo-keto reductase family 1 member B8 (Akr1b8). Activation of Nrf2 antioxidant pathway was evident in astrocytes by increased cellular redox and mitochondrial membrane potentials, elevated glutathione and ATP levels and resistance against H_2O_2 treatment. In vivo, DMF induced NQO1 in lymphoid organs and Akr1b8 in gastrointestinal tissues in wild type mice and rats for up to 24 h. The dependency of oxidative protection on Nrf2 was confirmed in vitro by silencing of Nrf2 transcription with specific siRNA and in vivo by the lack of a pharmacodynamic response in $Nrf2^{-}/^{-}$ mice.

DMF also significantly diminished excitotoxic lesion volume (44 and 61 %, at DMF doses of 75 and 100 mg/kg, respectively) and improved neuronal survival as well as functional neurological deficits (41 % at 100 mg/kg DMF) following intrastriatal malonate injection in rats.

In an experimental autoimmune encephalomyelitis (EAE) disease model of MS rats, DMF dose-dependently inhibited disease symptoms (demyelination and cellular degeneration), with a partial reduction at 100 mg/kg DMF and complete abrogation at 200 mg/kg DMF. Twice daily instead of once daily dosing improved efficacy of the 100 mg/kg to a level similar to the 200 mg/kg dose. Prolonged DMF treatment for 32 days induced antioxidant pathway genes NQO1 and Akr1b8 to levels comparable to those of healthy rats.

DMF and MMF were also found to exert anti-inflammatory activity as shown by suppression of LPS-mediated induction of inflammatory cytokines in vitro (TNF_{α}, IL1β, CXCL10, CCL4). This anti-inflammatory effect relied on Nrf2 at low levels of DMF or MMF, but became independent at high concentrations, in macrophages from WT and $Nrf2^{-}/^{-}$ mice.

In rat collagen-induced arthritis model, DMF reduced inflammation and inflammatory cell infiltration by inhibiting pro-inflammatory cytokine expression and activation of macrophages. Likewise, DMF also exerted anti-inflammatory activities in rat EAE model by inhibition of activation of astrocytes, macrophages and microglia.

2.3.2.2. Secondary pharmacodynamic studies

These studies were not performed by the applicant and this was considered acceptable by the CHMP on the basis of the overall non clinical findings.

2.3.2.3. Safety pharmacology programme

Cardiovascular system

DMF and MMF at 60, 180, 600 and 1500 µM (n = 3 or 4) did not significantly inhibit the hERG channel (≤3.6% and ≤1.2%, respectively), and the IC50 was considered to be >1500 µM. At doses of 60, 600 and 1500 µM, DMF and MMF did not alter cardiac conduction of canine Purkinje fibres.

In telemetered dogs treated with vehicle on Day 1 and 10, 100, and 1000 mg/kg DMF on Days 6, 8, and 12, vomiting was observed in all animals at doses > 100 mg/kg/day. Elevated heart rate was also noted from approximately 3 hours post-dosing and lasted until 9-12 hours post-dose. Mean arterial blood pressure in the animals treated with the 100 and 1000 mg/kg dose levels decreased to approximately 90 to 100 mmHg at 3 hours post dose, as compared to the controls (approximately 100 to 120 mm Hg) and remained approximately 10 to 15 mmHg below the vehicle control animal levels through 13 to 15 hours post dose. The time period of elevated heart rates and decreased arterial blood pressures was similar in all of the animals treated with DMF, suggesting that these observations were related to treatment. There were no effects of DMF on the QT interval on ECG corrected for heart rate (QTc), and no ECG abnormalities, even at supra-therapeutic doses up to 1000 mg/kg.

Respiratory system

In telemetered dogs (same in vivo study evaluating cardiovascular effects as described above), no effects on respiratory rate, peak thoracic pressure were noted.

Central Nervous system

These studies were performed using Fumaderm, which contains as main constituent DMF (56 %). When tested after oral administration of Fumaderm up to 464 mg/kg, DMF did not show pharmacological effects on motility, nociceptive behaviour, sleeping time, body temperature.

2.3.2.4. Pharmacodynamic drug interactions

These studies were not performed by the applicant and this was considered acceptable by the CHMP, on the basis of the available clinical data on drug interactions.

2.3.3. Pharmacokinetics

The pharmacokinetics and metabolism of DMF were investigated using the following animal species: rats, dogs and monkeys.

After oral administration, DMF was rapidly absorbed and converted pre-systemically to monomethyl fumarate (MMF) with T_{max} of 0.5 to 1 h rats, and 0.5 to 2 h in dogs. The clearance of MMF was also rapid as evident by half-lives of around 1.3 h in rats and up to 1 h in dogs. Direct administration of DMF to sites of the intestinal tract indicated predominant absorption of DMF in duodenum and jejunum. Gender differences in pharmacokinetic profile were apparent in rats only with about 1.7-fold higher exposure of females compared to males. In dogs, compared to extended release formulations, the DMF commercial formulation (enteric-coated microtablets) revealed rapid absorption (T_{max} 1.13 h) higher exposure (C_{max} 6.16 µg/ml; AUC_{inf} 7.91 µg·h/ml) and accelerated elimination ($t_{1/2}$ 0.517 h). After repeated doses of 5, 50, 75 and 100 mg/kg in dogs, MMF exposure (AUC_{last}) generally increased dose-dependently. C_{max} at all dosages and AUC of the 75 mg/kg group were less than dose-proportional and both $t_{1/2}$ and Cl/F appeared to be independent of dose. In the toxicology studies, the overall exposure (AUC and C_{max}) of MMF increased dose proportionally in all species after repeated administration. In rats, the higher exposure of females than in males was also evident in toxicokinetic determinations. No accumulation was observed across species.

Independently of the DMF dose, MMF was found to have a very low binding to proteins in rats, dogs, monkeys, and human plasma. Most significant binding was noted to human plasma proteins (unbound 55.1-66.1 %), whereas substantial lower binding was observed in dogs and monkeys (unbound 76-78.7 % and 90-100 %, respectively) and even complete absence of binding was found in rats.

After oral administration in rats, ^{14}C-labelled DMF widely distributed outside the gastrointestinal tract reaching maximum levels in kidneys, glandular tissues and brain.

In rats, DMF was subject to extensive metabolism and was predominantly eliminated by exhalation of CO_2 (60.9 % in males, 64.5 % in females). The main metabolite in plasma could be identified as glucose, whereas the combination of fumaric acid and citric acid was also detected at prominent levels. These findings suggested DMF and MMF metabolic pathway involved esterases and production of fumaric acid that is likely to enter into the highly conserved tricarboxylic acid (TCA) cycle leading to generation of water, CO_2 and glucose. Due to rapid DMF transformation to other metabolites, a minor amount of the radioactive DMF dose (< 0.2 %) was found to be excreted unchanged in urine. About 21 % of the DMF radioactive dose was determined in urine. Cysteine and N-acetyl cysteine conjugates of mono- and dimethyl succinate were the major metabolites in urine, whereas MMF represented only up to 1.7 % of the radioactive dose. Faecal elimination was negligible (≤ 4.4 %). No gender differences were observed in the metabolic profile of DMF and all metabolites identified in humans were found in rats.

MMF has been shown not to induce or inhibit many of the major human CYP enzymes (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4). In vitro studies using Caco-2 cells also indicated that DMF was not a substrate or an inhibitor of P-gp.

2.3.4. Toxicology

2.3.4.1. Single dose toxicity

Acute toxicity studies were performed in mice and rats using oral and intraperitoneal (i.p) routes.

In mice, the No Observed Effect Level (NOEL) was 316 mg/kg for both routes, whereas in rats, the NOEL was 681 mg/kg for males and 316 mg/kg for females. The estimated lethal dose in 50% of animals (LD_{50}) was slightly higher in males (920 mg/kg i.p., 1200 mg/kg p.o in mice , 910 mg/kg i.p., 3220 mg/kg p.o in rats) as compared to females (990 mg/kg i.p., 1340 mg/kg p.o. in mice, 820 mg/kg i.p., 2630 mg/kg p.o in rats).

In mice, clinical signs of reduced motility, ataxia, dyspnoea, cyanosis, muscular hypotonia were observed at oral doses as low as 681 mg/kg. Ataxia and hypopnoea were observed at i.p doses as low as 464 mg/kg.

In rats, ataxia, muscular hypotonia, inhibited respiratory rate and motility were noted at oral doses as low as 2610 mg/kg. Reduced food intake and decreased body weight gain were seen at 1470 and 2150 mg/kg, respectively. Ataxia, muscular hypotonia, reduced motility and respiratory rate were also observed at i.p. doses as low as 681 mg/kg. Dyspnea (825mg/kg); tremor, pilo-erection (1000 mg/kg); abdominal positioning (1470 mg/kg) were also noted.

In these studies, the kidneys, forestomach and liver were identified as target organs of DMF-toxicity.

2.3.4.2. Repeat dose toxicity

Repeat-dose studies have been conducted in mice, rats, dogs, and monkeys using the oral route. In mice, doses were ranging from 50 to 400 mg/kg in both studies of 4 and 13 week durations. In rats, doses were ranging from 50 to 500 mg/kg (3 months) and 25 to 200 mg/kg (6 months). In dogs, doses ranged from 25 to 125 mg/kg (18 days, dose ranging), 50 to 250 mg/kg (4 week, comparison to Fumaderm) and 5-75 mg/kg (11 months). In monkeys, doses ranged from 5 to 125 mg/kg (2 weeks) and 5 to 75mg/kg (12 months). Animals were dosed with either DMF formulated in 0.8% aqueous hydroxypropyl methylcellulose (in mice, rats and monkeys) or the clinical capsule (in dogs).

Oral tolerability

Oral tolerability was tested using DMF as a suspension or as a capsule. In rats, oral tolerability was below 500 mg/kg. In dogs, oral administration of DMF as a suspension was limited to less than 100 mg/kg due to persistent emesis. As an oral capsule, dogs administered DMF at 75 mg/kg/day presented with persistent emesis and body weight loss, resulting in reducing the high dose to 50 mg/kg/day at day 7 in the 11 month study. In monkeys, 75 mg/kg/day was the oral MTD for DMF.

Laboratory findings

In dogs, changes in haematological and clinical chemistry parameters as well as reduced thymus weights with lymphoid atrophy were seen at ≥ 50 mg/kg/day DMF in the 28 day study. In this study, a pronounced decrease in body weight and food consumption was also noted in animals. This may have contributed to the observed changes. In addition, reversible signs of anaemia and increased extramedullary haematopoiesis were detected at ≥ 200 mg/kg/day in the 13 week study in mice and sporadic but significant alterations in haematological and clinical chemistry parameters were noted at ≥ 50 mg/kg/day in the 3 months study in rats. These alterations were considered as incidental findings.

Renal findings

The kidney was clearly identified as target organ of DMF toxicity in all four species tested in toxicity studies: mice, rats, dogs, and monkeys. These effects have been observed at low doses, without any safety margin towards human therapeutic doses. In mice, increase in kidney weights was noted. In rats, nephrotoxicity was observed in repeat-dose studies (4 week, 3 and 6 months). In the 2-year carcinogenicity studies in rats and mice, nephrotoxicity was also seen. In dogs, hypertrophy and regeneration of the cortical tubular epithelium were noted in males, whereas both sexes revealed dilation of cortical tubules, atrophy of the cortical parenchyma, infiltration of mixed inflammatory cells in the renal papilla and hyperplasia of papillary urothelial cells. These alterations were observed at all dosages and were still evident in one or more animals per DMF-treated group at the end of the recovery period. In monkeys, kidney alterations corresponded to single cell necrosis and regeneration of the cortical tubular epithelial cells with a higher incidence and severity in the 75 mg/kg/day group. These DMF-related changes were similarly present in animals of the 25 and 75 mg/kg groups at the end of the recovery period. Mild to moderate interstitial renal fibrosis were also noted at recovery necropsy, indicative of irreversible loss of tissue and function, accompanied by cortical tubular atrophy in male monkeys of the high dose group. These findings were associated with increases of BUN by 42-77 % and of creatinine by 22-56% in one animal.

Forestomach findings

In mice and rats, the forestomach (non-glandular stomach) has been identified as a target organ for DMF toxicity. This effect was observed at all doses administered across the toxicology studies performed in these species, including the 2-year carcinogenicity studies. Common findings were increased stomach weights, hyperplasia, hyperkeratosis, inflammation, and ulceration which a trend for reversal. In rats, squamous cell carcinoma was observed in the forestomach of one of 30 males and one of 30 females that had received 250 mg/kg DMF for 3 months. In addition, literature data suggested that activation of the Nrf2 pathway may induce severe hyperkeratosis in the oesophagus and forestomach of mice (Motohashi *et al*, 2004). It is known that the forestomach lacks a clear anatomical counterpart in non-rodent species including humans, although it is covered by oesophageal-type mucosa (Wester and Kroes, 1988). Nevertheless, food normally passes quickly through the oesophagus, hence contrasting its potentially prolonged residence in the rodent forestomach. In dogs, increased stomach erosions were determined in the 28 day study at 250 mg/kg/day DMF, which were not confirmed after chronic dosing of either the DMF capsule or HPMC formulation in dogs and monkeys, respectively. No oesophagus findings were observed in other toxicity studies in dogs and monkeys.

Liver findings

Hepatic effects were observed in the following species: mice, rats and dogs. Changes in liver function tests (LFTs) were not observed. However, no safety margins toward therapeutic human doses could be established. Liver to brain weight ratios were dose-dependently increased in the 3 months studies in mice (≥ 200 mg/kg/day) and rats (250 mg/kg/day) as well as in the 11 months study in dogs (≥ 50 mg/kg/day). In rats, minimal multifocal hepatic necrosis and bile duct hyperplasia were additionally observed in the 6 month study, predominantly females of the 100 and 200 mg/kg/day groups. At the end of the recovery period, minimal hepatic necrosis was still present in females at a lower incidence, whereas the bile duct hyperplasia completely reversed.

Testis findings

In the 11 month study in dogs, males showed decreased weights of testis and epididymis at the 75/50 mg/kg/day level. In addition, degeneration of the seminiferous tubular epithelium and presence of spermatid giant cells in the lumen of the seminiferous tubules were noted at 25 and 75/50 mg/kg/day dosages at the end of the treatment period, which could still be detected with decreased incidence and/or severity at the end of the recovery phase. In the epididymides,

hypospermia was observed in high dose males. DMF exposures as compared to human dose were approximately 3-and 7 fold higher and for hypospermia and epididymis, respectively, which were considered sufficient safety margins. Concomitantly, a pronounced decrease in body weight and food consumption was also noted in these animals. This may have contributed to the observed changes, because spermatogenesis in dogs has been reported to be non-specifically suppressed by starvation (Russell, 1990).

2.3.4.3. Genotoxicity

The mutagenicity and clastogenicity of DMF and MMF were evaluated using the standard test battery according to ICHS2A and B guidelines: Ames test in bacteria, chromosomal aberrations in CHO cells and human lymphocytes in vitro and rat micronucleus test in vivo. All of these studies had negative results.

2.3.4.4. Carcinogenicity

The oncogenic potential of DMF was assessed in mice and rats following oral administration for 2 years. Toxicities on the kidneys and forestomach observed in the previous toxicology studies were confirmed in these species.

In mice, neoplasias of the non-glandular forestomach were significantly increased at 200 and 400 mg/kg/day and slightly but not significantly at 75 mg/kg/day. Kidney tubular carcinomas were significantly increased in males at 200 and 400 mg/kg/day,, while adenomas were significantly increased in high dose females at 400 mg/kg/day. There was a slight but not significant increase in tubular carcinomas already in males of the 75 mg/kg/ day group. Males were also positive in the trend test for adenoma and carcinoma and females for adenoma.

In rats, hyperplasia of squamous epithelium of the forestomach with dose-dependent increase in squamous cell papilloma and carcinoma were detected. In addition, dose-dependent increases in epithelial degeneration and mineralization were observed in the glandular stomach of male and female rats and chronic inflammation in males. Kidney tubular carcinomas were also significantly increased in the 150 mg/kg/day high dose group in female rats, whereas renal tubular adenomas were found in males of this group with positive trend test. A slight but not significant increase in tubular carcinomas was already detected in female rats at 100 mg/kg/day.

In both mice and rats, a treatment and dose-related shift to chronic progressive nephropathy was observed in males and females.

2.3.4.5. Reproduction Toxicity

The effect of DMF on fertility, early embryonic and peri and post-natal development was assessed in male and female rats and in female rabbits.

In male rats, histopathological changes were observed in the testes at all doses tested in the fertility study. These effects included minimal to mild multifocal interstitial-(Leydig) cell hyperplasia. Testicular changes were also observed in the 2-year carcinogenicity study in rats, testicular Leydig cell hyperplasia and adenomas, and in the 11 month study in dogs, seminiferous tubule degeneration, spermatid giant cells and hypospermia of the epididymides (see 2.3.4.2). However, DMF had no effect on sperm count/motility or on fertility in male rats up to the highest dose tested (375 mg/kg). In female rats, the average number of estrous stages per 14 days was significantly reduced and the number of rats with prolonged diestrus was increased at the highest dose tested (250mg/kg), the female fertility and number of viable foetuses produced were not affected at this dose level.

In female rats and rabbits, MMF was shown to cross the placental membrane into foetal blood with a ratio of foetal to maternal plasma concentrations of 0.48 to 0.64 and 0.1, respectively. In the embryo-foetal development study in rats, maternal NOAEL was determined as 25 mg/kg due to maternal weight loss and reduced body weight gain. The developmental NOAEL was determined to be 100 mg/kg due to generally delayed foetal development as evident by decreases in foetal weight and increases in foetal alterations that were observed at higher exposures (delayed ossification in metatarsals and hindlimb phalanges). In the embryo-foetal development study in rabbits, four abortions were seen in the high dose group and maternal NOAEL was considered to be 25 mg/kg. No foetal developmental effects were observed. The developmental NOAEL was ≥ 150 mg/kg/day. No foetal malformations were noted in rats and rabbits.

In the pre- and postnatal development study in pregnant and lactating rats, DMF effects were limited to reduced body weights, and body weight gain. There was also a reduction in pup weights in the high dose group, and further evidence of stomach adverse effects were confirmed. As a result a NOAEL for maternal effects was determined as 25 mg/kg. No increased mortality due to DMF was observed. A NOAEL for viability and growth in the offspring was determined as 100 mg/kg due to reduction in pup body weights, and delays in sexual maturation in male rats at 250 mg/kg.

2.3.4.6. Toxicokinetic data

Toxicokinetic data on MMF was collected from all repeat-dose toxicology and the two year carcinogenicity studies with daily or BID (only dogs) administration, previously described. MMF was rapidly absorbed and eliminated in mice (T_{max} < 10 min; $t_{1/2}$ < 35 min), rats (T_{max} 25-45 min; $t_{1/2}$ ≤ 60 min), rabbits (T_{max} 25-42 min; $t_{1/2}$ ≤ 48 min), dogs (T_{max} < 0.5 to 4 h; $t_{1/2}$ 40 - 49 min) and monkeys (T_{max} < 1 h; $t_{1/2}$ 0.6 – 1.6 h). In addition, MMF levels generally increased in a dose-proportional manner. No relevant accumulation or gender differences were apparent in mice, dogs and monkeys. In contrast, female rats revealed higher MMF levels than males (by 8 % to 41 %).

In monkeys, potentially toxic DMF metabolites methanol and formic acid were studied. After half of the chronic toxicity study (Week 26), methanol AUC_{0-24h} was approximately 40 % higher in males of the 25 mg/kg group than in controls, and was present in both sexes at 75 mg/kg. At Week 52, methanol AUC_{0-24h} remained elevated to a smaller extent (~12 %) in males of the 75 mg/kg group, and not detectable in all other tested doses. No relevant differences were noted regarding formic acid exposure after DMF treatment.

2.3.4.7. Local Tolerance

No studies were performed by the applicant since the product is for oral use.

2.3.4.8. Other toxicity studies

No antigenicity, immunotoxicity and dependence studies were performed by the applicant and this was considered acceptable by the CHMP, given the claimed mechanism of action and findings in repeat dose toxicity studied in 4 different species. In addition, impurities were not studied since these are considered metabolites of DMF and hence already qualified in the toxicological program of DMF.

In rats, additional toxicity studies were performed with DMF treatment for up to 75 days to further evaluate the potential of DMF to induce renal toxicity. The following parameters were measured: kidney injury molecule-1 (KIM-1) and urinary albumin as complementary renal biomarkers to BUN and CREA levels for detection of tubular changes in the kidney, urinary total protein and

β2-microglobulin level for identification of glomeruli damage and impairment of tubular reabsorption (Dieterle *et al.,* 2010). Elevated levels of urinary albumin were found to be associated with the renal tubular changes observed after DMF treatment, whereas increases of Ki-67 were noted, possibly indicating enhanced proliferation due to regeneration. However, KIM-1 could not be clearly correlated with DMF-mediated nephrotoxicity and the short duration of these studies precluded manifestation of severe DMF-related renal effects, which were evident in previously described toxicology studies.

Combination studies were also submitted to further support the toxicology profile of DMF. Animal toxicity findings using DMF in combination with methotrexate were similar to the one observed using DMF alone. No exacerbation of these toxicities was noted after combination with methotrexate.

2.3.5. Ecotoxicity / environmental risk assessment

Table 1 Summary of main study results

Substance : dimethyl fumarate					
CAS-number (if available):624-49-7					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	cited value	0.77			Potential PBT No
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	0.77			not B
PBT-statement :	The compound is not considered as PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	default 3.6	µg/L			> 0.01 threshold Yes
Other concerns (e.g. chemical class)					No
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OPPTS 835.1110	K_{oc} = not detectable			substance not stable in water
Ready Biodegradability Test	OECD 109MS301	readily biodegradable			
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**valu e**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	Not valid	µg/l	Species: blue algae – test not valid
Daphnia sp. Reproduction Test	OECD 211	NOEC	55.9	µg/l	*Dapnia magna*
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	45.7	µg/l	Species: *Pimephales promelas*
Activated Sludge, Respiration Inhibition Test	OECD 209	EC 10	2000	µg/l	

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following point for further investigation:

- To repeat the Algae growth inhibition test (OECD 201)

2.3.6. Discussion on non-clinical aspects

In pharmacology studies, DMF and its primary active metabolite MMF were both able to trigger the activation of the Nrf2 antioxidant pathway. This mechanism is claimed to be associated with neuroprotective properties.

In the EAE models of MS in rats, DMF showed beneficial effects on demyelination and cellular degeneration and improved neurological deficits. In addition, in vivo studies indicated that DMF may act by reducing excitotoxic lesion volume and improving neuronal survival and functional outcome. However, the overall mechanism of action of DMF on MS is not fully understood. DMF was also found to exert anti-inflammatory activities by reducing inflammatory cell infiltration and inhibiting the induction of inflammatory cytokines and activation of astrocytes, macrophages and microglia.

No clinically relevant findings were evident in the safety pharmacology studies.

The results of the pharmacokinetic studies in animal showed: rapid oral absorption, extensive tissue distribution, very low protein binding and elimination by exhalation of CO_2. MMF, the main DMF metabolite, crosses the placental membrane into fetal blood. It is not known whether DMF drug material is excreted in milk.

Repeated dose studies identified the kidneys, forestomach and liver as main target organs for toxicity in animals.

Nephrotoxicity was detected in four different animal species and included renal tubule epithelial regeneration suggestive of injury. Such toxicity was also associated with renal tubular adenomas and carcinomas in mice and rats (see below). Increased liver weights were detected in mice, rats and dogs. Minimal multifocal hepatic necrosis and bile duct hyperplasia were also noted in rats. Given that no safety margins towards intended therapeutic levels in humans could be established across species (rats, dogs and monkeys), these findings were considered of potential clinical relevance. Findings in the forestomach of mice and rats consisted of squamous epithelial hyperplasia and hyperkeratosis, inflammation, and squamous cell papilloma and carcinoma in studies of 3 months or longer in duration. These findings were considered not relevant to humans, given the fact that the forestomach lacks a clear anatomical counterpart in non-rodent species and also considering the gastro-resistant pharmaceutical formulation applied for.

In the testes, degeneration of the seminiferous epithelium was seen in rats and dogs. Moreover, testicular interstitial (Leydig) cell hyperplasia and adenomas were found in the 2-year carcinogenicity study in rats at doses ≥ 100 mg/kg. The findings were observed at approximately the recommended dose in rats and 6 times the recommended dose in dogs (AUC basis). However, no effects were seen in the fertility study or upon chronic dosing in rats, as well as upon long-term dosing in mice (2 years) and monkeys (12 months). In addition, Leydig cell tumours in rats are commonly regarded to rely on exaggerated levels of luteinizing hormone, a mechanism to which humans appear to be relatively insensitive. This might explain the rarity of this type of tumour in humans including its absence in the clinical program of DMF and during post-marketing experience with Fumaderm as an oral treatment of psoriasis. In contrast, the testes findings in dogs showed reduced severity and incidence during the recovery phase and were attributed to the pronounced effect of DMF on body weight and food consumption, which required extra dietary supplementation. Moreover, a generally high background rate of spontaneous testicular lesions (20-30 %) has been determined in young dogs assigned to toxicology studies (Goedken, 2008). Thus, the testes findings in both species were considered of limited relevance to humans.

Carcinogenicity studies up to 2 years did show an increased incidence of renal tubular carcinoma in rats and mice confirming findings from repeated toxicity data. Contrary to the applicant view, the CHMP was not in agreement that these data were possibly due to exacerbation of age-related, species-specific rodent nephropathy.

There was no evidence of genotoxicity in a standard package of tests.

In male rats, DMF had no effect on sperm count/motility or on fertility in male up to the highest dose tested (375 mg/kg). In female rats, the average number of estrous stages per 14 days was significantly reduced and the number of rats with prolonged diestrus was increased at the highest dose tested (250mg/kg), the female fertility and number of viable foetuses produced were not affected at this dose level. In female rats and rabbits, MMF was shown to cross the placental membrane into foetal blood with a ratio of foetal to maternal plasma concentrations of 0.48 to 0.64 and 0.1, respectively. In the embryo-foetal development study in rats, maternal NOAEL was determined as 25 mg/kg due to reduced maternal body weight and body weight gain. The

developmental NOAEL was determined to be 100 mg/kg due to generally delayed foetal development as evident by decreases in foetal weight and increases in foetal alterations that were observed at higher exposures (delayed ossification in metatarsals and hindlimb phalanges). In the embryo-foetal development study in rabbits, four abortions were seen in the high dose group and maternal NOAEL was considered to be 25 mg/kg. No foetal developmental effects were observed. The development NOAEL was ≥ 150 mg/kg/day. No malformations were noted in rats and rabbits. In the pre-and postnatal development study, DMF effects were limited to reduced body weights, and body weight gain. There was also a reduction in pup weights in the high dose group, and further evidence of stomach adverse effects were confirmed. As a result a NOAEL for maternal effects was determined as 25 mg/kg. No increased mortality due to DMF was observed. A NOAEL for viability and growth in the offspring was determined as 100 mg/kg due to reduction in pup body weights, and delays in sexual maturation in male rats at 250 mg/kg. These reproductive toxicity findings were considered adequately described in the SmPC.

On the basis of the ERA data, the CHMP concluded that DMF is not expected to pose a risk for the environment.

2.3.7. Conclusion on the non-clinical aspects

Overall, the non-clinical aspects of DMF have been adequately documented and meet the requirements to support this application.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies in RRMS population – Table 2

Table 2

Parameters	Study Number			
	C-1900	Study 301	Study 302	Study 303
Number of Centers Locations	42 EU and Turkey	198 worldwide	200 worldwide	298 worldwide
Design	Randomized, double-blind, parallel-group, placebo-controlled, dose-ranging, efficacy and safety study	Randomized, double-blind, parallel-group, placebo-controlled, dose-comparison, efficacy and safety study	Randomized, double-blind, parallel-group, placebo and reference comparator, dose-comparison, efficacy and safety study	Randomized, double-blind, parallel-group, dose comparison, safety and efficacy study
Controls	Placebo	Placebo	Placebo Glatiramer acetate	N/A

Treatment Duration	1 year	2 years	2 years	Up to 5 years
Study Drug, Dose, Route, Regimen	BG00012 120 mg orally QD	-	-	-
	BG00012 120 mg orally TID	-	-	-
	-	BG00012 240 mg orally BID	BG00012 240 mg orally BID	BG00012 240 mg orally BID
	BG00012 240 mg orally TID	BG00012 240 mg orally TID	BG00012 240 mg orally TID	BG00012 240 mg orally TID
	-	-	Glatiramer acetate 20 mg SC injection QD	-
	Placebo orally TID	Placebo orally TID	Placebo orally TID	-

2.4.2. Pharmacokinetics

The phase I clinical pharmacology programme has been conducted using single or multiple doses of DMF, in healthy volunteers and MS subjects (including alcohol consumers). In total, 210 subjects were exposed to a single oral dose of DMF ranging from 120 to 360 mg DMF, and 149 subjects were exposed to repeated oral doses of DMF, including 48 patients with MS.

Concentrations of DMF and its analysed metabolites (e.g MMF, fumaric acid) were measured in plasma using HPLC-UV assay and LC-MS/MS methods in the PK studies. Pharmacokinetic parameters were determined using non compartmental models.

Absorption

Absolute bioavailability of DMF and MMF has not been evaluated. In a few healthy subjects, the absorption of DMF was rapid as the maximum plasma concentrations of DMF-derived radioactivity occurred with one hour. Less than 1% of the total administered radioactivity was found in the faeces indicating that the drug was essentially completely absorbed. The enteric-coating of the microtablets has shown to delay the onset of absorption and slow the overall rate of absorption resulting in a longer lag time, however Cmax of MMF is increased about 40%.

Prolonged lag time and Tmax were also noted with food intake, from 0.25-0.75 h to 2 to 2.5 h and from 2-2.5 h to 4-6 h intervals, respectively. Under fed conditions, Cmax decreased and a slight increased AUC, suggesting no clinically significant effect on exposure of DMF, when taken with food. These findings appeared to be correlated with a lower AE incidence, when compared to fasting state, notably for flushing events, 94% versus 68%.

PK data after single and multiple dosing were characterised by a high degree of inter-individual variability and irregular shape. Although the applicant has performed an extensive programme of physiologically based pharmacokinetic simulations to support a better understanding of the high inter-subject variability in the PK profile of BG00012, further investigation on the model and its mechanistic background is recommended by including different transit times of the particles and a more thorough matching of in vitro to in vivo dissolution profiles.

In MS subjects, the median Tmax values for MMF were 5 hours (BID) and 7.5 hours (TID), whereas the median Cmax values were 1.72 mg/L (BID) and 1.93 mg/L (TID). The overall MMF exposure was dose proportional with median $AUC_{(0-24)}$ values of 8.02 h.mg/L (BID) and 12.3 h.mg/L (TID). The MMF concentrations returned to below detection at the end of the 24-hour dosing period before the first dose on the next day, and no accumulation was observed on a daily basis with 4 days of dosing. The lack of carry-over concentrations at the end of the dosing period, and the reproducibility of the PK profiles over the 24-hour dosing cycle with both the BID and TID regimens for up to 4 days, indicated that the PK of BG00012 is unchanged with multiple dosing.

Distribution

In healthy subjects, the apparent volume of distribution after administration of BG00012 240mg was 64.07 L (23.870) and 72.69 L (43.521) with BG00012 360 mg, in the fasted state. In MS patients who received BG00012 240 mg BID or TID with food, the apparent volume of distribution was 134.58 L and 117.02 L. MMF did not preferentially partition or sequester into the cellular components of blood and red blood cells, red blood cell to plasma partition coefficients and whole blood to plasma partition coefficients were <1. Human plasma protein binding of DMF was in the 58% - 69% range at the doses of 10,5 and 1.25 µg/mL. MMF had a lower range of binding in plasma of approximately 30 to 40 %.

Elimination

Exhalation of CO2 was found as the primary route of dimethyl fumarate elimination accounting for 60% of the dose. Renal and faecal elimination were secondary routes of elimination, accounting for 15.5% and 0.9% of the dose respectively.

The terminal half-life of MMF was generally short in the 0.5-1.2 h.

Dose proportionality and time dependencies

Dose proportionality for AUC was confirmed in single and multiple dose studies across the 120 mg to 360 mg dose range studied. Although inter-subject variability was observed for Cmax, this was considered not clinically significant. Potential covariates (gastric PH, sex, age, weight and food intake), affecting the exposure, did not influence safety and efficacy outcomes in subgroup of patients included in Phase III studies.

There was no accumulation following multiple dosing.

Special populations

No specific studies have been conducted in special populations.

Gender and age had a marginal impact on Cmax only, suggesting no clinically significant impact on the pharmacokinetics of DMF.

No relevant effect of alcohol consumption was found, when taken with DMF. However, the release of drug may be accelerated in the presence of alcohol.

Since the renal pathway is a secondary route of elimination for dimethyl fumarate accounting for less than 16% of the dose administered, evaluation of pharmacokinetics in subjects with renal impairment was not conducted.

As dimethyl fumarate and monomethyl fumarate are metabolised by esterases, without the involvement of the CYP450 system, evaluation of phamacokinetics in subjects with hepatic impairment was not conducted. However considering the presence of cysteine and N-acetylcysteine conjugates in urine, the mechanism of metabolic conversion of MMF remains unclear. An effect of hepatic impairment on the pharmacokinetic of DMF cannot therefore be completely ruled out.

Based on the results of Analysis of Variance (ANOVA), body weight is the main covariate of exposure (by Cmax and AUC) in relapsing remitting multiple sclerosis (RRMS) subjects, but did not affect safety and efficacy outcomes in subgroup of patients included in Phase III studies.

No data are available in the paediatric population as the clinical study included in the PIP has been deferred. The elderly population was also not studied and no data are available.

Pharmacokinetic interaction studies

The potential interactions were studied in humans for the following drugs: glatiramer, interferon beta-1a.

In addition, an interaction study was conducted to determine the safety, tolerability, and pharmacokinetics (PK) of different doses and dosing regimens of BG00012 administered with and without non enteric coated acetylsalicylic acid (ASA) compared to placebo in healthy subjects.

When co-administered with interferon beta-1a 30 µg IM injection, the pharmacokinetic profile of oral BG00012 240 mg TID was not affected. However, an increased AEs reporting was noted using the combination : 71% subjects in the group receiving BG00012 alone reported AEs as compared to 100 % subjects in the group receiving both BG00012 and interferon beta-1a. Similar findings were noted in the interaction study evaluating the pharmacokinetic profile of BG0012 240 mg TID, when co-administered with glatiramer 20 mg SC injection. No relevant pharmacokinetic interaction was found, however, one subject was withdrawn from the study after receiving BG00012 with GA due to mild nausea and 84% of subjects who received BG00012 alone reported an adverse event compared to 92 % of subjects who received the combination BG00012 plus GA..

325 mg of acetylsalicylic acid, when administered approximately 30 minutes before BG00012 at doses ranging from 240 mg BID to 360 mg TID, and at 120 mg every hour for 3 consecutive hours in the morning and again in the evening, had no effect on the PK profile of BG00012.

No interaction study was performed with oral contraceptives, given DMF lack of interactions with CYPs. However the CHMP considered it necessary to complement the available in vitro data by a clinical study, in view of the reproductivity toxicity findings (see 2.3.4.5). The SmPC of DMF is not recommending oral contraceptives as a method of birth control.

Pharmacokinetics using human biomaterials

In vitro studies did not suggest inhibition properties for DMF or MMF on the following CYPs: 2D6, 3A4, 2B6, 2C8, 1A2, 2C9, 2C19 and 2E1. No inducing effect was also observed on the following CYPs: 1A2, 2B6, 2C8, 2C9, 2C19 and 3A4. MMF was not found to act as an inhibitor of several studied transporters (Pgp, BCRP, or BSEP OCT1, OCT2, OAT1, OAT3, OATP1B1, OATP1B3, MATE1, and MATE2K).

2.4.3. Pharmacodynamics

Mechanism of action

Two clinical studies further investigated the claimed mechanism of action of DMF via activation of the NrF2 antioxidant pathway. These included patients with rheumatoid arthritis (RA) and RRMS.

In RA patients, the median NAD(P)H dehydrogenase quinone 1, NQO-1 levels (adjusted for housekeeping gene beta-2 microglobulin [B2M]) were increased at both Weeks 2 and 12 compared to the placebo group, and the increases at Week 12 were statistically significant: 36.4% change from baseline BG00012 TID versus -1.6% placebo. In the BG00012 BID group, there was a

statistically significant increase in NQO-1 level at Week 12 (18.3% change from baseline versus 1.6% placebo). No significant changes were observed for heme oxygenase-1 (HO-1).

In RRMS patients, median percent change in NQO-1 levels relative to baseline were upregulated at both Week 12 and Week 48 compared to the placebo group, and both increases were statistically significant: 15.6% and 14.0% change from baseline in BG00012 BID group versus 4.5% and 0.0% placebo group at Weeks 12 and 48 respectively, and 29.0% and 13.1% change from baseline in BG00012 TID group versus (vs) 4.5% and 0.0% placebo group at Weeks 12 and 48, respectively. No significant change was seen for HO-1.

Primary and Secondary pharmacology

Pharmacodynamic effects of DMF on the heart have been investigated in healthy subjects. In addition, the potential cause of BG00012-mediated flushing and GI symptoms was evaluated by examining the effect on concentrations of PGD2 and/or its metabolites in plasma and/or urine and other prostaglandins, as well as other biomarkers (e.g., serotonin and histamine, and tumor necrosis factor or TNFα) in psoriasis and healthy subjects with/ without pre-treatment with ASA. Some of these studies were previously discussed in relation to the pharmacokinetic profile of DMF.

In a specific study in healthy volunteers, single doses of BG00012 240 mg and 360 mg, did not reveal any significant differences in the QTc interval, when compared to placebo.

In psoriasis subjects, an increase in PGD2 and PGF2α levels was observed during the flush for both groups, one treated with a single oral dose of 240 mg BG00012, the other taking an oral dose of 120 mg BG00012 TID . Plasma serotonin concentrations also increased for both groups. The plasma levels of histamine and TNFα were not influenced by the occurrence of flushing.

In healthy subjects taking 325 mg ASA (30 minutes prior to BG00012 administration), the incidence and intensity of flushing were reduced. In this study, flushing was related to MMF exposure, but a clear association between the severity of flushing and serum levels of MMF was not established. For all treatment groups, the incidence of flushing AEs was highest on Day 1 of dosing and decreased over time. Most subjects had flushing episodes on 2 or 3 days of dosing, and only a few patients had flushing on all 4 days of dosing. Mean Global Flushing Severity Scale (GFSS) scores were mild for all groups throughout the study; these were highest on Day 2 (following Day 1 dosing) and decreased over time for all treatment groups. Overall FSS scores for all treatment groups were mild, were highest on Day 1, and decreased over time. The low incidence and mild scores for the GI effects measured by Overall GI Symptom Scale (OGISS), the Acute GI Symptom Scale (AGIS), and the Bowel Movement Questionnaire (BMQ) precluded definitive conclusions regarding the relationship between PK parameters and GI symptoms.

2.4.4. Discussion on clinical pharmacology

The pharmacokinetic profile (absorption, distribution, metabolism and elimination) of DMF was characterised by a high degree of inter-individual variability and irregular shape. This may be related to stomach transit differences, although the underlying mechanism is not fully understood (see 2.4.5). DMF did not seem to interact with several CYPs and transporters (including P-gp), suggesting minimal role of the liver on its metabolism.

Using the enteric coated microtablets, a delay of onset and slow rate of absorption was achieved, thus improving the tolerability profile of DMF, considering the product is associated with GI and flushing events (see 2.6).

Under fed conditions, Cmax decreased and a slight increased AUC was noted, suggesting no clinically significant effect on exposure of DMF, when taken with food. These findings appeared to be correlated with a lower AE incidence, when compared to fasting state, notably for flushing

events. The SmPC of DMF recommends that it should be taken with food due to improved tolerability with respect to these AEs.

There was no indication of differences in the pharmacokinetic profile of BG00012 between MS patients and healthy volunteers.

Bioequivalence has been demonstrated between the 120 mg and the 240 mg capsules in the fasted state.

No specific studies have been conducted in patients with renal and hepatic impairment. Considering that DMF is primarily metabolised via esterases and does not appear to involve CYP450 system or renal pathway as a main route of elimination, the absence of those studies were accepted and no dose adjustments are recommended for these patients. However, considering the presence of cysteine and N-acetylcysteine conjugates in urine, the mechanism of metabolic conversion of MMF remains unclear. An effect of hepatic impairment on the pharmacokinetic of DMF cannot therefore be completely ruled out. The CHMP therefore recommended to include a warning for patients with severe renal or hepatic impairment as a precautionary measure. In addition, long term data is intended to be collected in the observational study to monitor the safety profile in these patients (see 2.6).

No data are available in the paediatric population as the clinical study included in the PIP has been deferred. The elderly population was also not studied and there was a limited exposure to patients aged 55 years or above. Age had a marginal impact on Cmax only, suggesting no clinically significant impact on the pharmacokinetics of DMF. No dosage adjustment is recommended for the elderly population.

No relevant effect of alcohol consumption was found, when taken with DMF. However, the release of drug may be accelerated in the presence of alcohol. Such information has been included in the SmPC, given the occurrence of GI events, which may be increased in case of consumption of large quantities of undiluted strong alcoholic drinks, defined as more than 30% alcohol by volume.

When co-administered with either interferon beta-1a and glatiramer, the pharmacokinetic profile of DMF was not altered, however an increased AE reporting was noted.

No in vivo interaction study was performed with oral contraceptives, in the absence of in vitro interactions with CYPs. However the CHMP considered necessary to complement these data by a clinical study, in view of the reproductivity toxicity findings (see 2.3.4.5). The SmPC of DMF is not recommending oral contraceptives as method of birth control.

In addition, in view of safety profile observed in the main RRMS studies (see 2.6), the absence of interaction studies with anti-neoplastic or immunosuppressive therapies, vaccines is reflected in the SmPC.

Single doses of DMF did not affect the QTc interval.

In psoriasis subjects, an increase in PGD2 and PGF2α levels was observed during the flush, however, the plasma levels of histamine was not influenced by the occurrence of flushing, suggesting that hypersensitivity is unlikely to play a main role.

In healthy volunteer subjects, administration of 325 mg ASA, 30 minutes prior to BG00012 reduced flushing severity and further supported a prostaglandin-mediated flushing mechanism. No conclusions could be drawn on the mechanistic profile of the GI events, given their low incidence during the study. Overall, the CHMP considered that the data are still limited and the underlying mechanism of flushing and GI events is not completely understood. Results on an ongoing dose titration study with ASA are awaited to further address this issue, although the CHMP noted that additional investigations may need to be considered on the basis of the expected data.

2.4.5. Conclusions on clinical pharmacology

Overall, the pharmacological profile of DMF in human studies has been adequately characterised for its intended use. The CHMP considered necessary to address the missing information on interaction with oral contraceptives as part of the risk management plan (see 2.8).

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following point for further investigation:

- To further investigate the model used to understand the high inter-subject variability in the PK profile of BG00012 and its mechanistic background by including different transit times of the particles and a more thorough matching of in vitro to in vivo dissolution profiles.

2.5. Clinical efficacy

The following indication was initially applied for: disease modifying therapy in adult patients with relapsing multiple sclerosis to reduce the frequency of relapses and to delay the progression of disability.

The clinical development program comprises the following clinical studies:

- a phase II, 48 week (1 year), multicenter, double blind, randomised, placebo-controlled, parallel-group study **(C-1900)** evaluating efficacy and safety of DMF versus placebo in patients with relapsing remitting multiple sclerosis. This study included two parts: a 24-week double-blind, placebo-controlled safety and efficacy phase (Part 1) followed by a 24-week dose-blinded, safety extension phase (Part 2).

- a phase III, 96 week (2 years), multicenter double-blind, randomised, placebo-controlled, parallel group study (**109MS301**) evaluating the efficacy and safety of BG00012 240 mg BID and 240 mg TID administered orally versus placebo in patients with relapsing-remitting multiple sclerosis.

- a phase III, 96 week (2 years), multicenter double-blind, randomised, placebo-controlled, parallel group study (**109MS302**) evaluating the efficacy and safety of BG00012 240 mg BID and 240 mg TID administered orally versus placebo and glatiramer acetate in patients with relapsing-remitting multiple sclerosis.

Another study (**109MS303**) is currently ongoing. The study is a multicenter, randomised, dose blind, parallel group, 5 year extension study evaluating the long term efficacy and safety of BG00012 240 mg BID and 240 mg TID administered orally in patients with relapsing-remitting multiple sclerosis.

2.5.1. Dose response study

One dose ranging study (C-1900) using either 120 mg QD BG00012 (120 mg), 120 mg TID BG00012 (360 mg), 240 mg TID BG00012 (720 mg) was performed including a total number of randomised patients of 257 patients (n=64 for each of the DMF groups, n=65 for placebo group).

During the double blind placebo controlled phase, all patients from the 240 mg TID group received BG00012 120 mg TID for 1 week and then increased to 240 mg TID for the remainder of dosing. During the dose-blinded, safety extension phase, all patients who received BG00012 in Part 1 continued on the same dosing regimen, while patients who received placebo in Part 1 switched to BG00012 120 mg TID escalating to 240 mg TID after 1 week. The population studied had RRMS with a rather mild disease form with a median baseline Expanded Disability Status Scale (EDSS) score of 2.5 and a median number of relapses in the last year of 1.0. The majority (64%) were

women, and of Caucasian race (98%). The mean age was around 36, the mean duration of the disease was 6 years.

Analyses on MRI endpoints (primary/secondary) were performed in the Efficacy Evaluable (EE) population. The ITT population was used for the analysis on clinical endpoints (secondary) such as the ARR and disability progression as measured by the EDSS score.

The highest dose, 240 mg TID of BG00012 showed statistically significant differences in comparison to placebo for the primary endpoint, the total number of new gadolinium (Gd)-enhancing lesions over 4 scans at Weeks 12, 16, 20, and 24 (calculated as the sum of these 4 MRI scans) and all secondary MRI endpoints including mean cumulative number of new Gd-enhancing lesions over the placebo-controlled phase ($p=0.002$), the number of new or newly enlarging T2 hyperintense lesions($p<0.001$), and the number of new T1 hypointense lesions ($p=0.014$). There was a clear difference in efficacy between the BG00012 240 mg TID dose group compared to the 120 mg QD and the 120 mg TID treatment groups as both of these lower doses did not demonstrate any significant effect in the EE population when compared to placebo for any MRI endpoints. For the primary analysis, the total number of new Gd-enhancing lesions accumulated over 4 scans from Week 12 through Week 24 by was reduced by 69% ($p<0.001$) for the 240 mg TID group.

No statistically significant differences were found for any of the BG00012 treatment groups in comparison to placebo on the ARR, the proportion of relapse-free patients or the EDSS score. Generally, the annual relapse rate was rather low in all treatment groups and no clear dose relationship could be observed. During the placebo controlled phase, the adjusted ARRs in the ITT population were 0.65, 0.42, 0.78, and 0.44 in the placebo, the BG00012 120 mg QD, 120 mg TID, and 240 mg TID groups respectively. During the dose blinded extension phase, the ARRs for all treatment groups were 0.29, 0.26, 0.46 and 0.17 in the placebo/ BG00012 240 mg TID, the BG00012 120 mg QD, 120 mg TID, and 240 mg TID groups, respectively and thus were lower than in the initial phase. Similar positive trend was noted for the proportions of relapse-free patients which were greater during the extension phase. The best effect was achieved for the BG00012 120 mg QD with 78% relapse free patients. The change in EDSS score was rather small across all groups at all visits. However this might be expected given the short duration of the study.

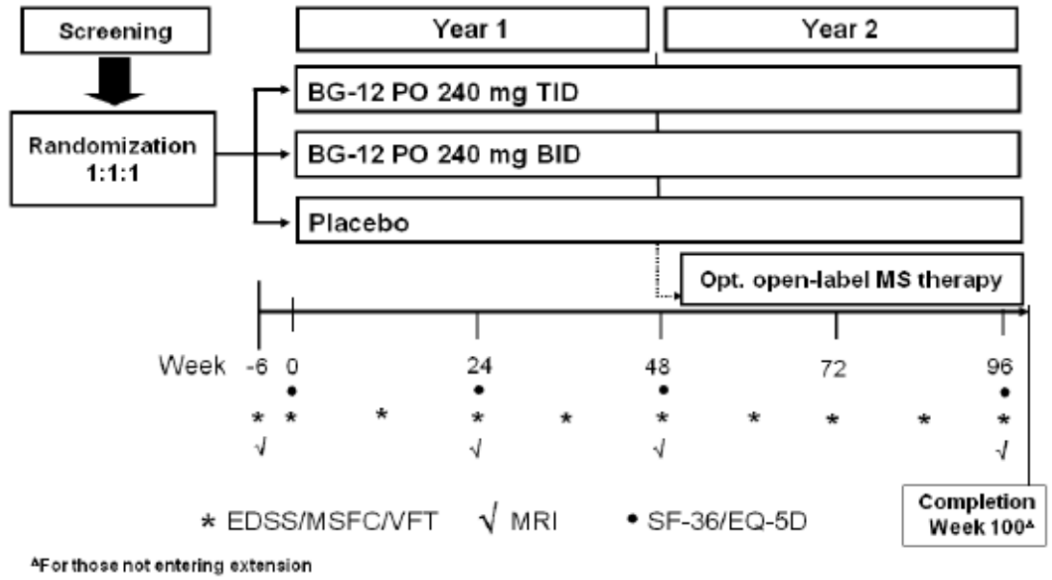
There were considerable imbalances at baseline for the mean number of Gd-enhancing lesions across the groups (notably in the 120 mg TID group which presented patients with higher disease activity i.e. higher number of Gd enhancing lesions). To further interpret the MRI results, subgroup analyses were added to the protocol after database lock by the applicant and additional sensitivity analyses were requested by the CHMP during the evaluation. In the CHMP requested analyses using the number of baseline Gd-enhancing lesions as covariates, BG00012 120 mg TID also provided statistically significant results for the primary endpoint ($p=0.009$). The mean total number of Gd-enhancing lesions was 1.7 and 1.1 for the 120 mg TID and the 240 mg TID treatment arm, respectively. Results were supported by analyses using other MRI endpoints (new or newly-enlarging T2 hyperintense lesions, number of new T1 hypointense lesions at Week 24. Hence, when correcting for the baseline number of Gd-enhancing lesions in the statistical models as a covariate, the effect of the 120 mg TID dosing regimen also reached statistical significance for the various MRI endpoints, at least in one of the requested models. However, the CHMP noted that this lower dose (120 mg TID) was no longer tested in the phase III studies. Dosing regimens of 240 mg BID and TID were subsequently used.

2.5.2. Main studies

2.5.2.1. Study 109MS301

This was a 96 week, double-blind, randomised, placebo-controlled, parallel group study evaluating the efficacy and safety of BG00012 240 mg BID and 240 mg TID administered orally versus placebo in subjects with relapsing-remitting multiple sclerosis (see Figure 1).

Figure 1



The study was conducted in a number of European countries and also in non-EU regions (e.g Switzerland, Canada, Australia, New Zealand, South Africa, Ukraine, Guatemala, India, Israel, Mexico, and the United States).

2.5.2.2. Methods

Study Participants

Main inclusion criteria

Males or females aged 18 to 55 years old, inclusive, at the time of informed consent; with a confirmed diagnosis of RRMS according to McDonald criteria #1-4 (as defined by Polman, 2005), a baseline EDSS score between 0.0 and 5.0, inclusive, at least 1 relapse within the 12 months prior to randomization and a prior brain MRI demonstrating lesion(s) consistent with MS, or with evidence of Gd-enhancing lesion(s) of the brain on an MRI performed within the 6 weeks prior to randomisation.

Male and female subjects of child bearing potential (including female subjects who were not post-menopausal for at least 1 year) must have been willing to practice effective contraception (as defined by the Investigator) during the study and been willing and able to continue contraception for 30 days after their last dose of study treatment.

Main exclusion criteria

These included: primary progressive, secondary progressive, or progressive relapsing MS ; inability to perform the Timed 25-Foot Walk (T25FW), Nine-Hole Peg Test (9HPT) with both upper extremities, and 3- Second Paced Auditory Serial Addition Test (PASAT 3), inability to perform

visual function tests (VFTs); history of malignancy, history of abnormal laboratory results indicative of any significant disease that would preclude participation in a clinical trial; history of clinically significant cardiovascular, pulmonary, gastrointestinal, dermatologic, psychiatric, neurologic (other than MS), and/or other major disease that would preclude participation in a clinical trial, history of human immunodeficiency virus (HIV) infection; an MS relapse that occurred within the 50 days prior to randomization and/or the subject had not stabilized from a previous relapse prior to randomization; positive for hepatitis C antibody and/or positive for hepatitis B surface antigen (HBsAg) at screening; any previous treatment with Fumaderm or BG00012, total lymphoid irradiation, Cladribine, T-cell or T-cell receptor vaccination, any therapeutic monoclonal antibody, with the exception of natalizumab; prior treatment with mitoxantrone or cyclophosphamide within 1 year prior to randomization; prior treatment with cyclosporine, azathioprine, methotrexate, natalizumab, mycophenolate mofetil, IV immunoglobulin, plasmapheresis or cytapheresis within the 6 months prior to randomization; prior treatment with subcutaneous or oral GA, Interferon-alpha or Interferon-beta within the 3 months prior to randomization; treatment with any of the following medications within the 50 days prior to randomization: steroids (IV or oral corticosteroid treatment, including agents that may act through the corticosteroid pathway [e.g., low dose naltrexone]) 4-aminopyridine or related products; treatment with another investigational drug or approved therapy for investigational use within the 6 months prior to randomization and current enrolment in any other investigational drug study or participation in any other investigational study within 6 months prior to randomization.

Treatments

Subjects were randomised to BG00012, given at an oral dose of 240 twice daily (BID), 240 mg 3 times daily (TID) or placebo. Subjects were randomly assigned to one of the 3 treatment group in a 1:1:1 ratio. Subjects in each group were to take 2 capsules of blinded study treatment orally TID, except during the first week, when they were to take 1 capsule orally TID. The duration of treatment was 96 weeks. Subjects who completed the treatment period and did not enter the extension study (109MS303) were to have their end-of-study visit 4 weeks later (Week 100). Rescue treatment options for subjects who relapsed or experienced confirmed disability progression (Lublin and Reingold, 2001; Polman et al., 2008) could be given. In particular, if a subject experienced a relapse at or after Week 24 that was confirmed by an independent committee of neurologists and the subject had received study treatment for at least 48 weeks, or if a subject experienced confirmed (12-week) disability progression at any time during the study, the subject was offered the option of continuing on blinded study treatment, switching to an approved, alternative MS medication while continuing to be followed in the study, or declining treatment with an approved, alternative MS medication while continuing to be followed in the study.

Objectives

The **primary objective** was to determine whether BG00012, when compared with placebo, was effective in reducing the proportion of relapsing patients at 2 years. The **secondary objectives** were to determine whether BG00012, when compared with placebo, was effective based on further clinical variables and MRI variables as defined in the secondary outcome measures. **Tertiary objectives** included the evaluation of the safety and tolerability of BG00012 and of its effect, when compared with placebo based on additional parameters as defined in the tertiary outcome measures.

Outcomes/endpoints

In general, for efficacy endpoints, 1 year refers to the Week 48 assessments, and 2 year refers to the Week 96 assessments.

Primary outcome measure

The primary endpoint was the proportion of Independent Neurology Evaluation Committee (INEC)-confirmed patients who experienced a relapse over the course of 2 years.

Secondary outcome measures

The secondary endpoints, which were assessed at 2 years, were: 1) the total number of new or newly enlarging T2 hyperintense lesions on brain MRI scans ; 2) the number of Gd-enhancing lesions on brain MRI scans; 3) the annualized rate of clinical relapses and 4) progression of disability that is sustained for 12 weeks as measured by either at least a 1.0 point increase on the EDSS score from baseline EDSS score ≥1.0, or at least a 1.5 point increase on the EDSS score from baseline EDSS score = 0.

Tertiary outcome measures

These included: Multiple Sclerosis Functional Composite Scale (MSFC) scores at 1 and 2 years; Visual Analogue Scale (VAS) score; SF-36 Health Survey (SF-36) score; EuroQol-5D (EQ-5D) score, proportion of subjects relapsed at 1 year; rate of clinical relapses at 1 year; number of relapses requiring intravenous (IV) steroid therapy; number of MS-related hospitalizations at 1 year and 2 years; total number of new T1 hypointense lesions on brain MRI scans at 1 and 2 years; volume of T1 hypointense lesions on brain MRI scans at 1 and 2 years; volume of T2 hyperintense lesions on brain MRI scans at 1 and 2 years; volume of Gd-enhancing lesions on brain MRI scans at 1 and 2 years; total number of new or newly enlarging T2 hyperintense lesions on brain MRI scans in at 1 year; number of Gd-enhancing lesions on brain MRI at 1 year, brain atrophy over 2 years; magnetization transfer ratio (MTR) in the whole brain at 1 and 2 years; change in PASAT 3, change in MSFC component from baseline to 1 and 2 years; time to onset of a 0.5 standard deviation (SD) worsening in the PASAT 3 that is sustained for 12 weeks , change in visual function from baseline to 1 and 2 years.

Sample size

A sample size of 337 per treatment group will have 90% power to detect a 30% reduction in the proportion of subjects relapsed at 2 years in each of the BG00012 groups compared with the placebo group, based on the Chi-square test. This calculation assumes that the estimates for proportion of subjects relapsed by 2 years are 48% for the placebo group and 33.6% for each of the BG00012 groups. It also assumes a drop-out rate of 23% over the 2 years and a 5% type I error rate.

Randomisation

It was performed in a 1:1:1 ratio and stratified by site using a centralised interactive voice response system (IVRS).

Blinding (masking)

Placebo and BG00012 capsules were identical in size, shape, colour, and taste. All study staff was blinded to the subjects' randomized treatment assignments for placebo and BG00012. Also, to prevent site personnel from observing any drug-induced symptoms (e.g., flushing), subjects were instructed not to take their dose of study treatment within 4 hours before a clinic visit. Efficacy measures were assessed by a blinded examining neurologist, with routine neurological care and safety measures assessed by a separate treating neurologist. The roles of the examining and treating neurologists were not interchangeable. All relapses were confirmed by a INEC, and all MRI scans were read in a blinded manner at independent central laboratories for the evaluation of radiological endpoints.

Statistical methods

ITT, PP populations and MRI cohort (defined as all subjects in the ITT population who consented to participate in the MRI and had any MRI data recorded) were used for efficacy analysis. . The ITT population was the primary population for the analysis of efficacy endpoints.

For all primary and secondary endpoints the two BG00012 treatments were compared with placebo in order to test the hypothesis that the active treatment was statistically superior to placebo. For each primary and secondary endpoint a number of sensitivity analyses were pre-specified in order to confirm the robustness of the results. To control the Type I error set at 5%, a hierarchical testing scheme was pre-specified in which for each endpoint, beginning with the primary and followed by the secondary endpoints, in an pre-defined order, the two active BG00012 treatments were tested in the following order: BG00012 240 mg TID versus placebo; BG00012 240 mg BID versus placebo. In this closed testing scheme the second dosing regimen (BID) was only tested statistically if the first dosing regimen (TID) had achieved statistical superiority at the two-sided 5% level of significance. Furthermore each secondary endpoint was only tested if all previous endpoints in the pre-defined order had demonstrated statistical superiority for both dosing regimen. This closed testing procedure was used in order to control for multiplicity.

In the primary analyses of all efficacy endpoints except for that of confirmed disability progression based on EDSS scores, observed data after alternative MS medications were initiated were excluded, or subjects were censored at the time of the alternative medication initiation. Missing post-baseline MRI data were imputed, using the subject's observed post-baseline data, on the assumptions that new lesions develop at a constant rate. Missing data were not imputed for subjects with no post-baseline measurements.

The primary and secondary efficacy endpoints were also analysed for the following pre-specified subgroups: baseline EDSS score (EDSS ≤2.0 versus EDSS >2.0); age (age <40 versus age ≥40); gender; region; baseline weight (by quartiles); baseline number of relapses (≤1 and ≥2); baseline McDonald criteria (1 versus 2, 3, and 4); prior treatment with a medication for MS (Yes versus No); MRI cohort (Yes versus No); baseline Gd-enhancing lesions (absent or present), MRI cohort only; baseline T2 hyperintense volume (above or below median), MRI cohort only.

No interim analyses were conducted.

The primary efficacy endpoint, the proportion of subjects relapsed at 2 years, was analysed by the Cox proportional hazards model for the time to first relapse (prior to initiation of rescue medication), adjusted for treatment, region, number of relapses in the one year prior to study entry, baseline age (<40 versus ≥40 years), and EDSS score (≤2.0 versus >2.0). The proportion of subjects who experienced a relapse over the 2-year period was estimated as the cumulative probability of relapse from the Kaplan-Meier curve of the time to first relapse during the study (i.e., the Kaplan-Meier product-limit estimator). If there were no early withdrawals during the study, the Kaplan-Meier estimate of the proportion of subjects relapsed at 2 years is the same as the observed proportion of subjects relapsed by 2 years. Since the proportion of subjects who experienced a relapse was estimated from the Kaplan-Meier curve, the treatment groups were compared using a Cox proportional hazards model for the time to the first relapse. In addition to the estimated proportion of subjects relapsed at 2 years, the estimated proportions of subjects relapsed at 24 weeks, 48 weeks (1 year), and 72 weeks were presented. Sensitivity analyses were performed using different definitions of relapse (e.g., objective relapses) or different populations (e.g., per-protocol population), or included data after subjects switched to alternative MS medication. Additional sensitivity analyses also used logistic regression.

The four secondary endpoints were tested in the following pre-specified order: 1) total number of new or newly enlarging T2 hyperintense lesions on brain MRI scans at 2 years (MRI cohort); 2)

total number of Gd-enhancing lesions on brain MRI scans at 2 years (MRI cohort); 3) annualized relapse rate at 2 years and 4) progression of disability at 2 years.

The annualized relapse rate for each treatment group was estimated in three ways. However all statistical inference was based on the adjusted rate obtained from a generalised linear model in which the number of relapses was adjusted for covariates that were considered to be important predictors of response. Therefore the annualized relapse rate at 2 years was analyzed using a negative binomial regression model adjusted for baseline EDSS score (≤2.0 versus>2.0), baseline age (<40 versus ≥40 years), region, and the number of relapses in the year prior to study entry.

Disability progression measured by EDSS over 2 years was analysed using a Cox proportional-hazards model and Kaplan-Meier curves. Progression based on 12-week confirmation and 24-week confirmation was also analysed. Subjects who did not have a sustained progression were censored for the analysis.

Negative binomial regression was used to analyse the number of new or newly-enlarging T2 hyperintense lesions and the number of new T1 hypointense lesions over 2 years. Ordinal logistic regression was used for the analysis of the number of Gd-enhancing lesions at 2 years.

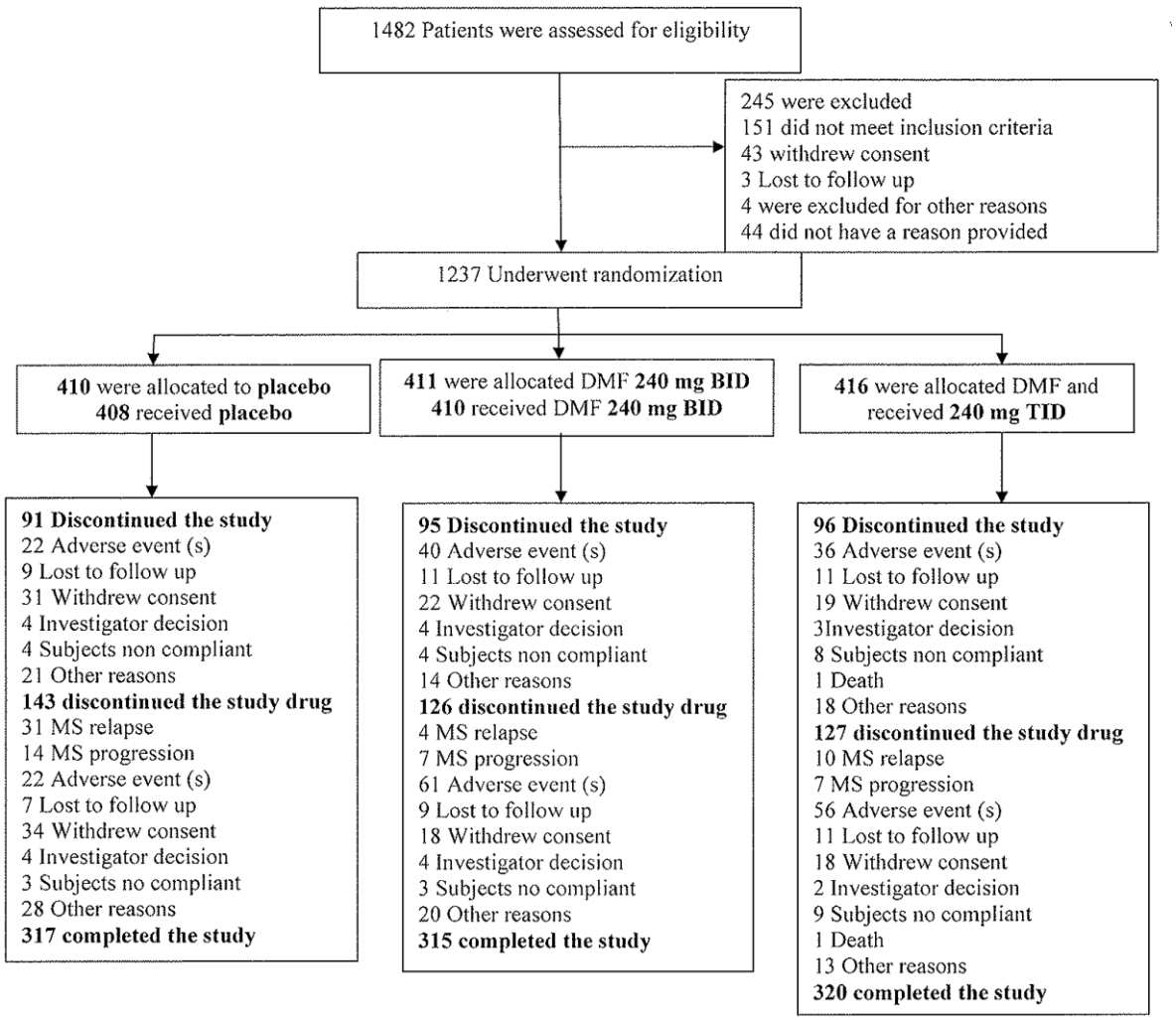
GCP issues were identified with three of the centres; the 23 patients from these sites were included in the ITT population and sensitivity analyses were also conducted excluding these patients.

Results

Participant flow

This is presented in Figure 2.

Figure 2



Recruitment

The first subject was treated on 14 March 2007, and the last subject received his or her last dose on 10 February 2011. The last subject completed the study on 23 February 2011.

Conduct of the study

The five protocol amendments prior to database lock were related to the study design and evaluation. These included revision of the objectives (rank order, secondary/tertiary endpoints were interchanged regarding the reduction of the annualized relapse rate at 1 year and at 2 years), increased safety monitoring (review of the cardiovascular risk factor at entry), increasing sites and country specific amendments related to provision of interferon beta-1a (Avonex).

Baseline data

These are summarised in Table 3.

Table 3

	Placebo	DMF 240 mg BID	DMF 240 mg TID	Total
Number of patients, ITT population	**408**	**410**	**416**	**1234**
Age (years, median)	39	38	39	39
Min, Max	18,56	18,55	18,56	18,56
% Age< 40/ ≥40	50/50	55/45	51/49	52/48
% females/males	75/25	72/28	74/26	74/26
Race (% white)	78	78	79	79
MRI cohort (% inclusion)	180 (44)	176 (43)	184 (44)	540 (44)
Weight (Kg, median)	68.5	67	69	68
Min, Max	37,137.7	35,142.5	42,140.5	35,142.5
Baseline McDonald Criteria (%)	**N=408**	**N=410**	**N=416**	**N=1234**
1(a)	338 (38)	336 (82)	326 (78)	1000 (81)
2(b)	54 (13)	52 (13)	62 (15)	168 (14)
3(c)	9 (2)	16 (4)	21 (5)	46 (4)
4(d)	7 (2)	6 (1)	7 (2)	20 (2)
Time since first MS symptoms (years)	**n=408**	**N=410**	**N=416**	**N=1234**
Mean	8.5	8.5	7.8	8.3
SD	6.84	6.79	6.32	6.65
Median	7.0	7.0	6.0	7.0
Min, Max	0,32	0,42	0,32	0,42
Time since MS diagnosis (years)	**n=408**	**N=410**	**N=416**	**N=1234**
Mean	5.8	5.6	5.1	5.5
SD	5.78	5.39	5.29	5.49
Median	4.0	4.0	3.0	4.0
Min, Max	0,31	0,32	0,23	0,32
EDSS score	**N=408**	**N=409**	**N=416**	**N=1233**
Mean	2.48	2.40	2.36	2.42
SD	1.241	1.290	1.188	1.240
Median	2.50	2.00	2.00	2.00
Min, Max	0.0,6.0	0.0,6.5	0.0,6.0	0.0,6.5
Number of relapses within the previous 3 years	**N=407**	**N=410**	**N=416**	**N=1233**
Mean	2.5	2.5	2.4	2.5
SD	1.56	1.44	1.27	1.43
Median	2.0	2.0	2.0	2.0
Min, Max	0,12	0,11	0,7	0,12
Number of relapses within the past year	**N=408**	**N=410**	**N=416**	**N=1234**
Mean	1.3	1.3	1.3	1.3
SD	0.67	0.67	0.60	0.65
Median	1.0	1.0	1.0	1.0
Min, Max	0,4	0,6	0,4	0,6

	Placebo	DMF 240 mg BID	DMF 240 mg TID	Total
Number of patients, MRI cohort	**180**	**176**	**184**	**540**
Nb of Gd lesions	**N=180**	**N=175**	**N=184**	**N=539**
Mean	1.6	1.2	1.2	1.4
SD	3.45	3.30	4.10	3.64
Median	0.0	0.0	0.0	0.0
Min, Max	0,26	0,23	0,46	0,46
Volume of Gd lesions mm^3	**N=180**	**N=175**	**N=184**	**N=539**
Mean	155.4	220.7	147.0	173.7
SD	329.82	737.85	488.52	542.70
Median	0.0	0.0	0.0	0.0
Min, Max	0,2475	0,5273	0,4812	0,5273
Nb of T2 lesions	**N=180**	**N=176**	**N=184**	**N=540**
Mean	49.2	47.6	55.8	50.9
SD	38.60	34.70	44.31	39.56
Median	39.0	40.5	43.5	41.0
Min, Max	0,194	0,222	0,220	0,222
Volume of T2 lesions mm^3	**N=180**	**N=176**	**N=184**	**N=540**
Mean	6524.9	8463.8	9014.5	8005.2
SD	7601.50	10058.73	11769.21	10010.78
Median	3735.0	4766.5	5074.0	4572.0
Min, Max	0,52568	9,59561	0,98850	0,98850
Nb of T1 hypotense lesions	**N=180**	**N=176**	**N=184**	**N=540**
Mean	27.3	27.8	33.6	29.6
SD	28.47	29.66	34.74	31.19
Median	18.0	19.5	21.5	19.0
Min, Max	0,170	0,240	0,202	0,240
Volume of T1 hypointense lesion mm^3	**N=180**	**N=175**	**N=184**	**N=539**
Mean	2224.5	3076.5	3300.4	2868.4
SD	3979.07	4685.27	4986.47	4587.14
Median	924.5	1236.0	1386.5	1167.0
Min, Max	0,39456	0,26209	0,33514	0,39456
Normalised whole brain volume mm^3	**N=179**	**N=176**	**N=184**	**N=539**
Mean	1586703.1	1573521.6	1565496.8	1575159.7
SD	81675.68	85817.60	93139.54	87349.69
Median	1596621.9	1578651.9	1578370.6	1582536.4
Min, Max	1361724,1752840	1362252,1772532	1308562,1747261	1308562,1772532
Median MTR whole brain	**N=147**	**N=152**	**N=149**	**N=448**
Mean	37.1	37.1	37.3	37.1
SD	5.72	6.05	6.06	5.94
Median	34.5	34.0	36.4	34.5
Min,Max	29,51	28,51	28,50	28,51

MS treatment history

This is presented in Table 4.

Table 4

	Placebo	BG00012 240 mg BID	BG00012 240 mg TID	Total
Number of subjects in ITT population	408 (100)	410 (100)	416 (100)	1234 (100)
Number of subjects who took any prior MS medication	227 (56)	223 (54)	230 (55)	680 (55)
Number of subjects who have taken the following medication prior to study entry				
INTERFERON BETA-1A	106 (26)	114 (28)	111 (27)	331 (27)
GLATIRAMER	75 (18)	52 (13)	60 (14)	187 (15)
INTERFERON BETA-1B	55 (13)	57 (14)	60 (14)	172 (14)
NATALIZUMAB	8 (2)	8 (2)	18 (4)	34 (3)
Any of above MS medications	172 (42)	162 (40)	168 (40)	502 (41)
Other	94 (23)	103 (25)	105 (25)	302 (24)
CORTICOSTEROIDS	33 (8)	34 (8)	41 (10)	108 (9)
AZATHIOPRINE	17 (4)	25 (6)	32 (8)	74 (6)
MITOXANTRONE	16 (4)	21 (5)	8 (2)	45 (4)
IMMUNOGLOBULIN G HUMAN	8 (2)	11 (3)	11 (3)	30 (2)
INTERFERON ALFA	12 (3)	9 (2)	5 (1)	26 (2)
METHOTREXATE	5 (1)	7 (2)	4 (<1)	16 (1)
METHYLPREDNISOLONE	4 (<1)	3 (<1)	6 (1)	13 (1)
PLASMAPHERESIS	2 (<1)	5 (1)	6 (1)	13 (1)
CYCLOPHOSPHAMIDE	3 (<1)	2 (<1)	4 (<1)	9 (<1)
INVESTIGATIONAL DRUG	3 (<1)	2 (<1)	3 (<1)	8 (<1)

Numbers analysed

In total, 99-100 % of randomised patients were included in the ITT and safety population. The 3 subjects who were not dosed were by definition not included in the ITT or safety populations. See Table 5.

Table 5. Number of Subjects in Each Treatment Group by Analysis Population

Population	Placebo	BG00012 240 mg BID	BG00012 240 mg TID	Total
Number of subjects randomized	410 (100)	411 (100)	416 (100)	1237 (100)
ITT population	408 (>99)	410 (>99)	416 (100)	1234 (>99)
Per-protocol population	381 (93)	350 (85)	359 (86)	1090 (88)
Safety population	408 (>99)	410 (>99)	416 (100)	1234 (>99)
MRI cohort	180 (44)	176 (43)	184 (44)	540 (44)

NOTE 1: Numbers in parentheses are percentages based on randomized subjects.
2: ITT population is defined as all subjects who were randomized and received at least 1 dose of study treatment (BG00012 or placebo).
3: Per-protocol population is defined as subjects from the ITT population without any major protocol violations.
4: Safety population is defined as all subjects who received at least 1 dose of study drug (including placebo and BG00012).
5: MRI cohort is defined as subjects from the ITT population, from sites selected to perform MRI assessment and have any MRI data.

Outcomes and estimations

Primary outcome measure

Results are summarised in Table 6 and Figure 3.

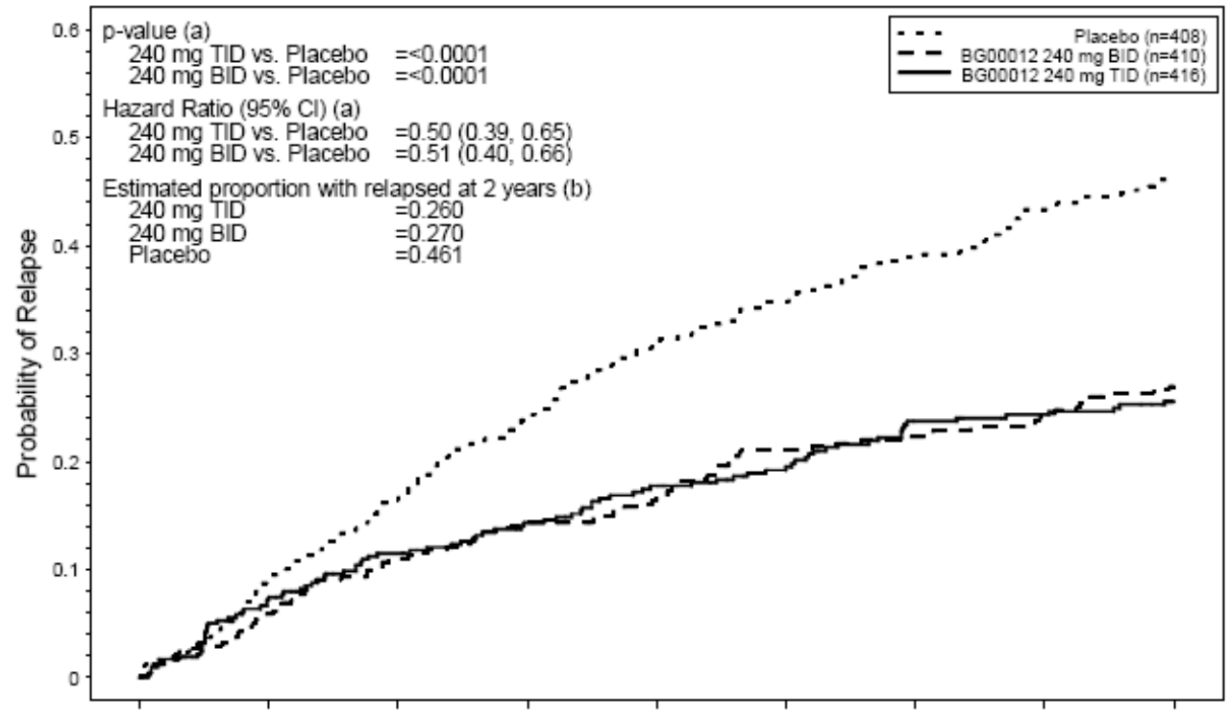
Table 6. Summary of proportion of subjects relapsed (INEC-confirmed relapses) at 2 years

	Placebo	BG00012 240 mg BID	BG00012 240 mg TID
Number of subjects in ITT population	408 (100)	410 (100)	416 (100)
Number of subjects relapsed			
Yes	171 (42)	98 (24)	95 (23)
No (Censored) (a)	237 (58)	312 (76)	321 (77)
Estimated proportion (b) of subjects relapsed at			
0 weeks	0.000	0.000	0.000
12 weeks	0.095	0.059	0.074
24 weeks	0.167	0.110	0.115
36 weeks	0.241	0.144	0.143
48 weeks	0.310	0.167	0.178
60 weeks	0.348	0.211	0.195
72 weeks	0.389	0.223	0.237
84 weeks	0.434	0.242	0.243
96 weeks (2 years, primary endpoint)	0.461	0.270	0.260
Number of subjects at risk (b)			
0 weeks	408	410	416
12 weeks	356	353	346
24 weeks	321	324	322
36 weeks	282	303	301
48 weeks	243	286	286
60 weeks	224	267	270
72 weeks	205	255	251
84 weeks	190	243	244
96 weeks	115	154	166
Time (weeks) to first relapse (b)			
10th percentile	13.57	22.00	20.14
25th percentile	38.00	87.00	91.00
50th percentile (Median)	NA	NA	NA
Hazard ratio (active/placebo) (95% CI) (c)		0.51 (0.40, 0.66)	0.50 (0.39, 0.65)
p-value (compared to placebo) (c)		<0.0001	<0.0001

NOTE 1: Only relapses confirmed by the INEC are included in the analysis.
2: Subjects who did not experience a relapse prior to switching to alternative MS medications or withdrew from study are censored at the time of switch/withdrawal.

(a) Subjects who did not have a relapse.
(b) Based on the Kaplan-Meier product limit method, up to 96 weeks.
(c) Based on Cox proportion hazards model, adjusted for baseline EDSS (<=2.0 vs >2.0), baseline age (<40 vs >=40), region and number of relapses in the 1 year prior to study entry.

Figure 3. Time to first relapse (INEC confirmed relapses) – ITT population



Number of Patients at Risk

Placebo	408	356	321	282	243	224	205	190	115
240 mg BID	410	353	324	303	286	267	255	243	154
240 mg TID	416	346	322	301	286	270	251	244	166

NOTE 1: Only relapses confirmed by the INEC are included in the analysis.
2: Subjects who did not experience a relapse prior to switching to alternative MS medications or withdrawal from study are censored at the time of switch/withdrawal.
(a) P-value and hazard ratio (active/placebo) are based on Cox proportional hazards model, adjusted for baseline EDSS (<=2.0 vs >2.0), baseline age (<40 vs >=40), region, and number of relapses in the 1 year prior to study entry.
(b) Kaplan-Meier estimate of the proportion of subjects relapsed within 2 years.

Secondary outcome measures

Results are summarised in Tables 7-10 and Figure 4.

Table 7. Number of New or Newly Enlarging T2 Lesions at 2 Years Compared to Baseline - MRI Cohort

	Placebo	BG00012 240 mg BID	BG00012 240 mg TID
Number of subjects in MRI cohort	180	176	184
Number of lesions			
0	45 (27)	68 (45)	62 (41)
1	8 (5)	26 (17)	28 (18)
2	3 (2)	14 (9)	11 (7)
3	8 (5)	10 (7)	5 (3)
>=4	101 (61)	34 (22)	46 (30)
n	165	152	152
Mean	16.5	3.2	4.9
SD	23.40	7.61	11.50
Median	7.0	1.0	1.0
25th, 75th percentile	0.0, 20.0	0.0, 3.0	0.0, 5.0
Min, Max	0, 106	0, 52	0, 106
Adjusted mean (a)	17.0	2.6	4.4
Lesion mean ratio (95% CI) (a)		0.15 (0.10, 0.23)	0.26 (0.17, 0.38)
% change (vs. placebo) and (95% CI) (a)		-85 (-90, -77)	-74 (-83, -62)
p-value (a)		<0.0001	<0.0001

NOTE 1: Numbers in parentheses are percentages.
2: Observed data after subjects switched to alternative MS medications are excluded. Missing data prior to alternative MS medications and visits after subjects switched to alternative MS medications are included and imputed using the constant rate assumption.
3: NS: Not statistically significant due to the closed testing procedure.
(a) Percentage change, 95% CI and p-value for comparison between the active and placebo groups, based on negative binomial regression, adjusted for region and baseline volume of T2 lesions.

Table 8. Number of Gd-Enhancing Lesions at 2 Years- MRI Cohort

	Placebo	BG00012 240 mg BID	BG00012 240 mg TID
Number of subjects in MRI cohort	180	176	184
Number of lesions			
0	103 (62)	142 (93)	130 (86)
1	16 (10)	8 (5)	10 (7)
2	13 (8)	1 (<1)	2 (1)
3-4	15 (9)	0	3 (2)
>=5	18 (11)	1 (<1)	7 (5)
n	165	152	152
Mean	1.8	0.1	0.5
SD	4.15	0.63	1.73
Median	0.0	0.0	0.0
25th, 75th percentile	0.0, 2.0	0.0, 0.0	0.0, 0.0
Min, Max	0, 30	0, 7	0, 15
Odds ratio (95% CI) (a)		0.10 (0.05, 0.22)	0.27 (0.15, 0.46)
p-value (a)		<0.0001	<0.0001

NOTE 1: Numbers in parentheses are percentages.
2: Observed data after subjects switched to alternative MS medications are excluded. Missing data prior to alternative MS medications and visits after subjects switched to alternative MS medications are included and imputed using the method of LOCF, or Next Observation Carried Backward (for skipped Week 24 visit).
(a) Odds ratio and p-value for comparison between the active and placebo groups, based on ordinal logistic regression, adjusted for region and baseline number of GD lesions.

Table 9. Summary of Annualized Relapse Rate (INEC-Confirmed Relapses) at 2 Years

	Placebo	BG00012 240 mg BID	BG00012 240 mg TID
Number of subjects in ITT population	408 (100)	410 (100)	416 (100)
Number of subjects with relapses of			
0	237 (58)	312 (76)	321 (77)
1	115 (28)	75 (18)	64 (15)
2	44 (11)	19 (5)	20 (5)
3	8 (2)	1 (<1)	9 (2)
>= 4	4 (<1)	3 (<1)	2 (<1)
Total number of relapses	246	128	140
Total number of subject-years followed	612.35	628.61	633.48
Unadjusted annualized relapse rate (a)	0.402	0.204	0.221
Adjusted annualized relapse rate (95% CI) (b)	0.364 (0.303,0.436)	0.172 (0.136,0.214)	0.189 (0.153,0.234)
Rate ratio (active/placebo) (95% CI) (b)		0.473 (0.365,0.613)	0.521 (0.404,0.670)
p-value (compared to placebo)		<0.0001	<0.0001
Subject relapse rate (c)			
n	408	410	416
Mean	0.550	0.242	0.244
SD	1.0230	0.6075	0.6188
Median	0.000	0.000	0.000
25th, 75th percentile	0.000, 0.584	0.000, 0.000	0.000, 0.000
Min, Max	0.00, 11.07	0.00, 4.87	0.00, 5.29

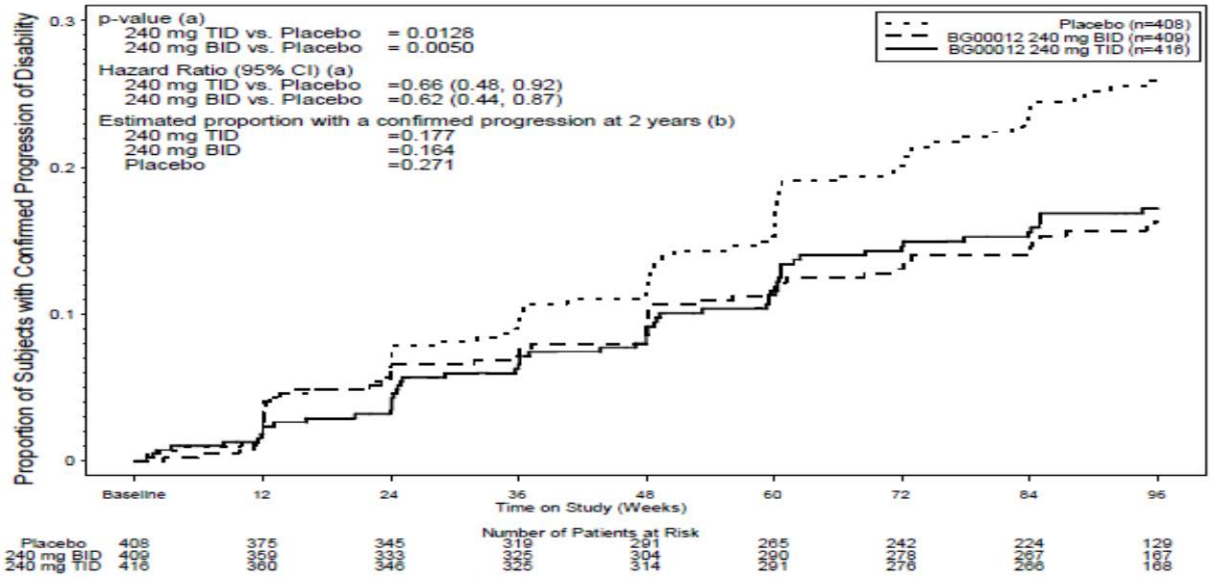
NOTE 1: Only relapses confirmed by INEC are included in the analysis.
2: Data after subjects switched to alternative MS medications are excluded.
3: Numbers in parentheses are percentages.
(a) The annualized relapse rate is calculated as the total number of relapses occurred during the study for all subjects, divided by the total number of subject-years followed in the study.
(b) Based on negative binomial regression, adjusted for baseline EDSS (<=2.0 vs >2.0), baseline age (<40 vs >=40), region and number of relapses in the 1 year prior to study entry.
(c) The number of relapses for each subject divided by the number of years followed in the study for that subject. Summary statistics across all subjects are presented.

Table 10. Summary of Time to Confirmed Progression of Disability at 2 Years as Measured by Increase in EDSS score (12 Weeks Confirmation)

	Placebo	BG00012 240 mg BID	BG00012 240 mg TID
Number of subjects in ITT population	408	410	416
Number of subjects in ITT population for EDSS (a)	408 (100)	409 (100)	416 (100)
Number of subjects progressed	89 (22)	57 (14)	62 (15)
Time (weeks) to progression (b)			
10th percentile	36.1	48.1	49.3
25th percentile	89.1	NA	NA
50th percentile	NA	NA	NA
Estimated proportion of subjects with progression at 2-years (b)	0.271	0.164	0.177
Hazard ratio (active/placebo) (95% CI) (c)		0.62 (0.44, 0.87)	0.66 (0.48, 0.92)
p-value (compared to placebo) (c)		0.0050	0.0128

NOTE 1: Confirmed progression of disability is defined as at least a 1.0 point increase on the EDSS from a baseline EDSS >=1.0 confirmed for 12 weeks or at least a 1.5 point increase on the EDSS from a baseline EDSS of 0 confirmed for 12 weeks.
2: Subjects are censored if they withdrew from study or switched to alternative MS medication without a progression.
3: Numbers in parentheses are percentages.
(a) Number of subjects in the ITT population with a baseline EDSS value.
(b) Estimated proportion of patients with progression and time to progression up to 96 weeks based on the Kaplan-Meier product limit method.
(c) Based on Cox proportion hazards model, adjusted for baseline EDSS, region and baseline age (<40 versus >=40).
Abbreviations: NA = not available since the proportion of subjects progressed within the 2-year follow-up is less than the specified percentage. NS = P-value <= 0.050 that is not considered statistically significant due to the closed testing procedure.

Figure 4. Time to Confirmed Progression of Disability as Measured by Increase in EDSS score (12 Weeks Confirmation) – ITT Population



NOTE: Confirmed progression of disability is defined as at least 1.0 point increase on the EDSS from a baseline EDSS >=1.0 confirmed for 12 weeks or at least a 1.5 point increase on the EDSS from a baseline EDSS of 0 confirmed for 12 weeks.
(a) P-value and hazard ratio (active/placebo) based on a Cox proportional hazards model, adjusted for age (<40 vs >=40), baseline EDSS and region.
(b) Kaplan-Meier estimate of the proportion of subjects confirmed progression within 2 years.

Tertiary outcome measures

Proportion of subjects relapsed over the first year was 31% in the placebo group, compared to 16.7% in the BG00012 BID group and 17.8% in the TID group. The hazard ratios were 0.49 for BG00012 BID versus placebo and 0.54 for BG00012 TID versus placebo (both p <0.0001).

The adjusted annualized rate of INEC-confirmed relapses over 1 year was 0.367 in the placebo group, compared with 0.183 in the BG00012 BID group and 0.207 in the BG00012 TID group. The hazard ratios were 0.50 for BG00012 BID versus placebo (p<0.0001) and 0.56 for BG00012 TID versus placebo (p =0.0002).

A total of 211 INEC-confirmed relapses required IV steroid therapy in the placebo group, compared to 111 and 114 in the BG00012 BID and TID groups, respectively. The adjusted annualized rate of relapses requiring IV steroids at 2 years was 0.310 in the placebo group, compared to 0.149 and 0.150 in the BG00012 BID and TID groups, respectively. The hazard ratios were 0.48 for BG00012 BID versus placebo (p<0.0001) and 0.49 for BG00012 TID versus placebo (both p <0.0001).

The adjusted annualized rate of MS-related hospitalization (ie relapses or other MS-related complications) at 2 years was 0.056 in the placebo group, compared with 0.036 and 0.030 in the BG00012 BID and TID groups, respectively. The rate ratios obtained from the model were 0.653 (p = 0.0708) for BG00012 BID versus placebo and 0.546 (p = 0.0125) for BG00012 TID versus placebo, representing reductions over placebo of 35% and 45%, respectively. BG00012 BID and TID reduced the annualized rate of MS-related hospitalizations over 1 year by 32% (p = 0.1633) and 48% (p = 0.0278), respectively.

At 2 years, improvement on MSFC composite z-score and individual components (PASAT 3, 9HPT, T25FW) and visual functions were observed for both BG00012 BID and TID groups however all the results were not statistically significant.

Proportion of subjects with confirmed progression of cognitive deficit at 2 years was 9.9% in the placebo group compared with 9.8% and 10.7% in the BG00012 BID and TID groups, respectively.

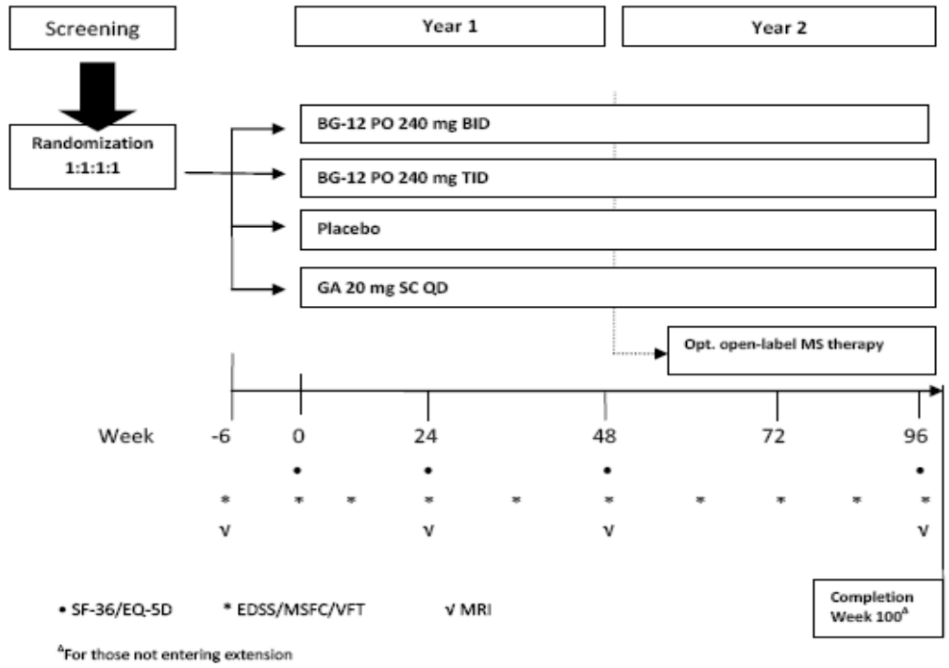
The hazard ratios obtained from the model were 1.04 (p = 0.8739) for BG00012 BID versus placebo and 1.10 (p = 0.6801) for BG00012 TID versus placebo.

Consistency with the clinical findings was also observed on the MRI tertiary endpoints, although all of these results were not statistically significant. Positive findings were also observed in the patient health reported outcomes.

2.5.2.3. Study 109MS302

This was a 96 week, multicenter double-blind, randomised, placebo-controlled, parallel group study evaluating the efficacy and safety of BG00012 240 mg BID and 240 mg TID administered orally versus placebo and glatiramer acetate in subjects with relapsing-remitting multiple sclerosis (see Figure 5).

Figure 5



The study was conducted in a number of European countries and also in non-EU regions (e.g Canada, Australia, New Zealand, Ukraine, Costa Rica, India, Israel, Mexico and the United States).

2.5.2.3.1. Methods

Study participants

Inclusion and exclusion criteria were the same as for those for study 109MS301 except that subjects previously treated with GA were excluded.

Treatment

Randomised patients were assigned in a ratio of 1:1:1:1 to receive: 1) Group 1: DMF 240 mg orally twice daily (2 capsules [120 mg each] BID and 2 placebo capsules QD); 2) Group 2: DMF240 mg TID (2 capsules [120 mg each] TID); 3) Group 3: Placebo (2 capsules TID) and 4) Group 4: GA (20 mg subcutaneous [SC] injection, QD). Hence, subjects in Groups 1, 2, and 3 were to take 2 capsules of blinded study treatment orally TID, except during the first week, when they were to take 1 capsule orally TID at 240 mg dose.

Objectives

The **primary objective** was to determine whether BG00012 was effective in reducing the rate of clinical relapses at 2 years. The **secondary objectives** were to determine whether BG00012, when compared with placebo, was effective based on further clinical variables and on MRI variables as defined in the secondary outcome measures. **Tertiary objectives** included the evaluation of the safety and tolerability of BG00012 and of its relative benefit risk versus placebo with GA versus placebo using mainly the same outcome measures as for study 109MS301.

Outcome measures

Primary outcome measures

The primary endpoint is the annualized relapse rate (ARR) at 2 years, which is evaluated as the number of relapses over the course of 2 years.

Secondary outcome measures

The secondary endpoints which were assessed at 2 years were:1) the total number of new or newly enlarging T2 hyperintense lesions on brain MRI scans, 2) the total number of new T1 hypointense lesions on brain MRI scans, 3) the proportion of subjects relapsed, 4) the progression of disability that is sustained for 12 weeks as measured by either at least a 1.0 point increase on the EDSS score from baseline EDSS score ≥1.0, or at least a 1.5 point increase on the EDSS score from baseline EDSS score = 0.

Sample size

It was anticipated that the annualized relapse rate in the placebo group would be approximately 0.61, while the rate on the BG00012 group would be approximately 0.456. A sample size of 308 subjects per group (BG00012 or placebo) would provide approximately 84% power to detect a 25% reduction in the annualized relapse rate at 2 years in the BG00012 group compared with the placebo group (difference between 0.61 and 0.456). A drop-out rate of 23% over 2 years was assumed. Due to the 1:1:1:1 randomization ratio, the GA group also had 308 subjects. The total planned sample size for the study was 1232.

Randomisation

It was performed in a 1:1:1:1 ratio and stratified by site using a centralised IVRS.

Blinding

Blinding methodology was the same as for study 109MS301 except that only the examining neurologist was blinded to treatment for all subjects, including for subjects who received GA.

Statistical methods

These were mainly the same as for study 109MS301 except that a separate but similar closed testing scheme was specified for comparing the single dose of glatiramer with placebo. However for BG00012 versus glatiramer, no formal hypothesis testing was intending for this comparison and the results were presented as estimates with associated 95% confidence intervals but no p-values were provided.

Results

Participant flow

This is presented in Figure 6.

1733 Patients were assessed for eligibility
303 were excluded
190 did not meet inclusion criteria
41 withdrew consent
5 Lost to follow up
4 refused to participate
7 were excluded for other reasons
56 did not have a reason provided
1430 Underwent randomization
363 were allocated and received placebo
362 were allocated DMF 240 mg BID
359 received DMF 240 mg BID
345 were allocated and received DMF 240 mg TID
360 were allocated GA
350 received GA
85 Discontinued the study
11 Adverse event (s)
11 Lost to follow up
14 Withdrew consent
6 Investigator decision
8 Subjects non compliant
1 Death
34 Other reasons
129 discontinued the study drug
18 MS relapse
8 MS progression
21 Adverse event (s)
7 Lost to follow up
14 Withdrew consent
3 Investigator decision
9 Subjects no compliant
49 Other reasons
278 completed the study
75 Discontinued the study
21 Adverse event (s)
9 Lost to follow up
9 Withdrew consent
2 Investigator decision
4 Subjects non compliant
30 Other reasons
106 discontinued the study drug
6 MS relapse
7 MS progression
36 Adverse event (s)
8 Lost to follow up
9 Withdrew consent
2 Investigator decision
4 Subjects no compliant
34 Other reasons
284 completed the study
72 Discontinued the study
26 Adverse event (s)
8 Lost to follow up
17 Withdrew consent
1 Investigator decision
3 Subjects non compliant
17 Other reasons
96 discontinued the study drug
3 MS relapse
5 MS progression
38 Adverse event (s)
4 Lost to follow up
15 Withdrew consent
1 Investigator decision
3 Subjects no compliant
27 Other reasons
273 completed the study
58 Discontinued the study
10 Adverse event (s)
11 Lost to follow up
17 Withdrew consent
2 Investigator decision
3 Subjects non compliant
1 Death
14 Other reasons
86 discontinued the study drug
6 MS relapse
8 MS progression
27 Adverse event (s)
8 Lost to follow up
10 Withdrew consent
2 Investigator decision
3 Subjects no compliant
1 Death
21 Other reasons
292 completed the study

Figure 6

Recruitment

The first subject was treated on 28 July 2007, and the last subject received the last dose on 04 August 2011. The last subject completed the study on 24 August 2011.

Conduct of the study

The three protocol amendments were related to the study design and evaluation. These included mainly increased safety monitoring (review of the cardiovascular risk factors, blood and urinary analysis to monitor renal function) and changes of eligibility for patients receiving approved open label MS therapy.

Of note, additional changes to the analysis described in the final SAP were as follows: the treatment effect of BG00012 versus GA for the primary and secondary efficacy endpoints was measured in terms of point estimates and 95% CIs to describe the variability about the estimated effects, however this comparison was not pre-specified; the analysis of MTR was planned in whole brain and in normal appearing brain tissue (NABT); however, the results for NABT were not reported by the MRI facility and therefore, these data were not included in the study database.

Baseline data

These are summarised in Table 11.

Table 11

	Placebo	**DMF 240 mg BID**	**DMF 240 mg TID**	**GA**	**Total**
Number of patients, ITT population	**363**	**359**	**345**	**350**	**1417**
Age (years, median)	37	38	38	36	37
Min, Max	18,56	18,55	18,55	18,55	18,56
% Age< 40/ ≥40	59/41	58/42	56/44	61/39	59/41
% females/males	69/31	68/32	72/28	71/29	70/30
Race (% white)	84	85	85	83	84
MRI cohort (% inclusion)	167(46)	169(47)	170(49)	175(50)	681(48)
Weight (Kg, median)	70	68.9	68.30	67.15	69.00
Min, Max	43,152.3	34,162.3	40,151	35.2,143.5	34,162.3
Baseline McDonald Criteria	**N=363**	**N=359**	**N=345**	**N=350**	**N=1417**
1(a)	309 (85)	291 (81)	284 (82)	294 (84)	1178 (83)
2(b)	37 (10)	38 (11)	40 (12)	32 (9)	147 (10)
3(c)	12 (3)	22 (6)	17 (5)	19 (5)	70 (5)
4(d)	5 (1)	8 (2)	4 (1)	5 (1)	22 (2)
Time since first MS symptoms (years)	**N=363**	**N=359**	**N=345**	**N=350**	**N=1417**
Mean	7.6	8.2	7.8	7.1	7.1
SD	5.98	6.89	6.70	5.92	6.39
Median	6.0	7.0	6.0	6.0	6.0
Min, Max	0,33	0,35	0,33	0,29	0,35
Time since MS diagnosis (years)	**N=363**	**N=359**	**N=345**	**N=350**	**N=1417**
Mean	4.8	4.9	4.6	4.4	4.7
SD	5.01	5.11	5.23	4.7	5.01
Median	4.0	3.0	3.0	3.0	3.0
Min, Max	0,33	0,30	0,27	0,24	0,33
EDSS score	**N=363**	**N=359**	**N=345**	**N=350**	**N=1417**
Mean	2.59	2.56	2.52	2.57	2.56
SD	1.170	1.202	1.185	1.223	1.194
Median	2.50	2.50	2.50	2.50	2.50
Min, Max	0.0,5.0	0.0,5.5	0.0,5.0	0.0,5.0	0.0,5.5

Number of relapses within the previous 3 years	**N=362**	**N=359**	**N=344**	**N=350**	**N=1415**
Mean	2.5	2.4	2.6	2.4	2.5
SD	1.46	1.27	1.50	1.32	1.39
Median	2.0	2.0	2.0	2.0	2.0
Min, Max	0,10	0,8	0,12	0,10	0,12
Number of relapses within the past year	**N=362**	**N=359**	**N=344**	**N=350**	**N=1415**
Mean	1.4	1.3	1.4	1.4	1.4
SD	0.80	0.63	0.72	0.64	0.70
Median	1.0	1.0	1.0	1.0	1.0
Min, Max	0,8	0,4	0,5	0,5	0,8

	Placebo	**DMF 240 mg BID**	**DMF 240 mg TID**	**GA**	**Total**
Number of patients, MRI cohort	**167**	**169**	**170**	**175**	**681**
Nb of Gd lesions	**N=166**	**N=168**	**N=166**	**N=175**	**N=675**
Mean (SD)	2.7	2.7	1.9	2.4	2.4
SD	7.71	6.22	5.02	6.81	6.51
Median	0.0	0.0	0.0	0.0	0.0
Min, Max	0,76	0,43	0,51	0,44	0,76
Volume of Gd lesions mm^3	**N=166**	**N=168**	**N=166**	**N=175**	**N=675**
Mean	226.3	290.9	235.0	311.8	266.7
SD	562.94	789.78	787.12	920.65	777.14
Median	0.0	0.0	0.0	0.0	0.0
Min, Max	0,3791	0,6462	0,7319	0,8114	0,8114
Volume of T2 lesions mm^3	**N=167**	**N=169**	**N=169**	**N=174**	**N=679**
Mean	14594.8	13876.2	12826.5	13788.8	13769.3
SD	13267.20	13347.74	13384.51	13562.13	13377.48
Median	10822.0	9701.0	7767.0	9434.5	9435.0
Min, Max	460,60595	136,76147	494,66553	333,72727	136,76147
Volume of T1 hypointense lesion mm^3	**N=166**	**N=168**	**N=166**	**N=175**	**N=675**
Mean	3722.2	3594.0	3135.0	3337.5	3446.1
SD	5261.88	5180.89	4606.49	4729.48	4944.61
Median	1762.5	1472.5	1368.0	1344.0	1509.0
Min, Max	0,32636	0,30903	0,32218	0,28852	0,32636
Normalised whole brain volume mm^3	**N=167**	**N=169**	**N=169**	**N=175**	**N=680**
Mean	1495774.5	1498017.2	1486525.9	1484361.3	1491096.1
SD	92758.98	97566.07	102741.07	138147.85	109523.39
Median	1493493.4	1513668.6	1489305.9	1489891.2	1496621.3
Min, Max	1176864,1788425	1181113,1740436	1196826,1760013	14737,1701118	14737,1788425
Median MRT whole brain	**N=157**	**N=154**	**N=157**	**N=163**	**N=631**
Mean	34.0	34.3	34.5	34.0	34.2
SD	6.00	6.03	6.15	5.70	5.96
Median	31.7	31.9	31.9	31.7	31.8
Min, Max	25,52	23,53	25,53	25,50	23,53

MS treatment history

This is presented in Table 12.

Table 12

	Placebo	BG00012 240 mg BID	BG00012 240 mg TID	GA	Total
Number of subjects in ITT population	363 (100)	359 (100)	345 (100)	350 (100)	1417 (100)
Number of subjects who took any prior MS medication	147 (40)	148 (41)	138 (40)	139 (40)	572 (40)
Number of subjects who have taken the following medication prior to study entry					
INTERFERON BETA-1A	80 (22)	66 (18)	70 (20)	76 (22)	292 (21)
INTERFERON BETA-1B	43 (12)	42 (12)	39 (11)	33 (9)	157 (11)
NATALIZUMAB	6 (2)	2 (<1)	6 (2)	2 (<1)	16 (1)
GLATIRAMER	1 (<1)	1 (<1)	3 (<1)	1 (<1)	6 (<1)
Any of above MS medications	111 (31)	101 (28)	100 (29)	103 (29)	415 (29)
Other	50 (14)	59 (16)	60 (17)	50 (14)	219 (15)
CORTICOSTEROIDS	22 (6)	24 (7)	17 (5)	26 (7)	89 (6)
PLASMAPHERESIS	7 (2)	9 (3)	9 (3)	8 (2)	33 (2)
MITOXANTRONE	5 (1)	5 (1)	7 (2)	7 (2)	24 (2)
AZATHIOPRINE	7 (2)	5 (1)	5 (1)	3 (<1)	20 (1)
INVESTIGATIONAL DRUG	5 (1)	5 (1)	5 (1)	2 (<1)	17 (1)
IMMUNOGLOBULIN G HUMAN	5 (1)	5 (1)	5 (1)	0	15 (1)
INTERFERON ALFA	2 (<1)	3 (<1)	6 (2)	4 (1)	15 (1)
METHYLPREDNISOLONE	2 (<1)	3 (<1)	4 (1)	3 (<1)	12 (<1)
METHOTREXATE	4 (1)	2 (<1)	2 (<1)	1 (<1)	9 (<1)

Number analysed

In total, 99-100 % of randomised patients were included in the ITT and safety population. One subject randomized to BG00012 240 mg TID actually received GA. For this reason, the distribution of subjects is different in the ITT (analyzed as randomized) and safety (analysed as treated) populations. Thirteen subjects (3 randomized to BG00012 BID and 10 randomized to GA) were randomized but not dosed and were, by definition, excluded from the ITT and safety populations. See Table 13.

Table 13. Number of Subjects in Each Treatment Group by Analysis Population

Population	Placebo	BG00012 240 mg BID	BG00012 240 mg TID	GA	Total
Number of subjects randomized	363 (100)	362 (100)	345 (100)	360 (100)	1430 (100)
ITT population	363 (100)	359 (>99)	345 (100)	350 (97)	1417 (>99)
Per-protocol population	351 (97)	332 (92)	303 (88)	337 (94)	1323 (93)
Safety population	363 (100)	359 (>99)	344 (>99)	351 (98)	1417 (>99)
MRI cohort	167 (46)	169 (47)	170 (49)	175 (49)	681 (48)

NOTE 1: Numbers in parentheses are percentages based on randomized subjects.
2: ITT population is defined as all subjects who were randomized and received at least 1 dose of study treatment (BG00012, placebo or GA).
3: Per-protocol population is defined as subjects from the ITT population without any major protocol violations.
4: Safety population is defined as all subjects who received at least 1 dose of study drug (including placebo, BG00012 and GA).
5: MRI cohort is defined as subjects from the ITT population, from sites selected to perform MRI assessment and have any MRI data.
6: One subject randomized to the BG00012 TID but took GA during the duration of the study and therefore, was counted in the GA group in the Safety population and was counted in BG00012 TID group in ITT population.

Outcomes and estimation

Primary outcome measure

Results are summarised in Table 14.

Table 14. Summary of Annualized Relapse Rate (INEC-Confirmed Relapses) at 2 Years

	Placebo	BG00012 240 mg BID	BG00012 240 mg TID	GA
Number of subjects in ITT population	363 (100)	359 (100)	345 (100)	350 (100)
Number of subjects with relapses of				
0	223 (61)	266 (74)	269 (78)	246 (70)
1	83 (23)	71 (20)	51 (15)	62 (18)
2	44 (12)	14 (4)	21 (6)	30 (9)
3	11 (3)	7 (2)	3 (<1)	8 (2)
>= 4	2 (<1)	1 (<1)	1 (<1)	4 (1)
Total number of relapses	212	124	106	163
Total number of subject-years followed	561.43	552.99	529.80	569.62
Unadjusted annualized relapse rate (a)	0.378	0.224	0.200	0.286
Adjusted annualized relapse rate (95% CI) (b)	0.401 (0.329,0.488)	0.224 (0.179,0.282)	0.198 (0.156,0.252)	0.286 (0.232,0.353)
Rate ratio (active/placebo) (95% CI) (b)		0.560 (0.423,0.740)	0.495 (0.369,0.662)	0.714 (0.548,0.931)
Percentage reduction (active vs. placebo) (95% CI) (b)		44.0 (26.0, 57.7)	50.5 (33.8, 63.1)	28.6 (6.9, 45.2)
p-value (compared to placebo)		<0.0001	<0.0001	0.0128
Subject relapse rate (c)				
n	363	359	345	350
Mean	0.497	0.266	0.315	0.351
SD	0.9014	0.5958	1.2002	0.8643
Median	0.000	0.000	0.000	0.000
25th, 75th percentile	0.000, 0.546	0.000, 0.526	0.000, 0.000	0.000, 0.540
Min, Max	0.00, 7.94	0.00, 5.14	0.00, 17.39	0.00, 10.15

NOTE 1: Only relapses confirmed by INEC are included in the analysis.
2: Data after subjects switched to alternative MS medications are excluded.
3: Numbers in parentheses are percentages.
(a) The annualized relapse rate is calculated as the total number of relapses occurred during the study for all subjects, divided by the total number of subject-years followed in the study.
(b) Based on negative binomial regression, adjusted for baseline EDSS (<=2.0 vs >2.0), baseline age (<40 vs >=40), region and number of relapses in the 1 year prior to study entry.
(c) The number of relapses for each subject divided by the number of years followed in the study for that subject. Summary statistics across all subjects are presented.
Abbreviations: NS = P-value <= 0.050 that is not considered statistically significant due to the closed testing procedure.

Secondary outcome measures

Results are presented in Tables 15-18 and Figures 7-8, in the order in which the endpoints were ranked.

Table 15. Number of New or Newly Enlarging T2 Lesions at 2 Years Compared to Baseline (MRI Cohort) – Primary Analysis

	Placebo	BG00012 240 mg BID	BG00012 240 mg TID	GA
Number of subjects in MRI cohort	167	169	170	175
Number of lesions				
0	17 (12)	38 (27)	43 (31)	36 (24)
1	7 (5)	24 (17)	21 (15)	22 (14)
2	4 (3)	16 (11)	13 (9)	12 (8)
3	5 (4)	11 (8)	12 (9)	9 (6)
>=4	106 (76)	51 (36)	51 (36)	74 (48)
n	139	140	140	153
Mean	19.9	5.7	5.1	9.6
SD	25.27	11.07	8.73	19.11
Median	11.0	2.0	2.0	3.0
25th, 75th percentile	4.0, 26.0	0.0, 5.5	0.0, 6.0	1.0, 9.0
Min, Max	0, 119	0, 84	0, 63	0, 119
Adjusted mean (95% CI) (a)	17.4(13.5,22.4)	5.1 (3.9, 6.6)	4.7 (3.6, 6.2)	8.0 (6.3,10.2)
Lesion mean ratio (95% CI) (a)		0.29(0.21,0.41)	0.27(0.20,0.38)	0.46(0.33,0.63)
% reduction (vs placebo) and (95% CI)(a)		71(59, 79)	73(62, 80)	54(37, 67)
p-value (a)		<0.0001	<0.0001	<0.0001

NOTE 1: Numbers in parentheses are percentages.
2: Observed data after subjects switched to alternative MS medications are excluded. Missing data prior to alternative MS medications and visits after subjects switched to alternative MS medications are included and imputed using the constant rate assumption.
(a) Percentage reduction, 95% CI and p-value for comparison between the active and placebo groups, based on negative binomial regression, adjusted for region and baseline volume of T2 lesions. NS: P-value <= 0.050 that is not considered statistically significant due to the applicable closed testing procedure.

Table 16. Number of New T1 Hypointense Lesions at 2 Years Compared to Baseline (MRI Cohort)– Primary Analysis

	Placebo	BG00012 240 mg BID	BG00012 240 mg TID	GA
Number of subjects in MRI cohort	167	169	170	175
Number of lesions				
0	29 (21)	55 (39)	61 (44)	53 (34)
1	8 (6)	21 (15)	21 (15)	19 (12)
2	10 (7)	15 (11)	19 (14)	22 (14)
3-4	29 (21)	12 (9)	9 (6)	18 (12)
>=5	63 (45)	37 (26)	30 (21)	42 (27)
n	139	140	140	154
Mean	8.1	3.8	2.7	4.5
SD	10.43	6.91	5.09	8.13
Median	4.0	1.0	1.0	2.0
25th, 75th percentile	1.0, 11.0	0.0, 5.0	0.0, 3.0	0.0, 5.0
Min, Max	0, 47	0, 47	0, 45	0, 47
Adjusted mean (95% CI) (a)	7.0(5.3,9.2)	3.0 (2.3, 4.0)	2.4 (1.8, 3.2)	4.1 (3.2, 5.3)
Lesion mean ratio (95% CI) (a)		0.43(0.30, 0.61)	0.35(0.24, 0.49)	0.59(0.42, 0.82)
% reduction (vs placebo) and (95% CI)(a)		57(39, 70)	65(51, 76)	41(18, 58)
p-value (a)		<0.0001	<0.0001	0.0021

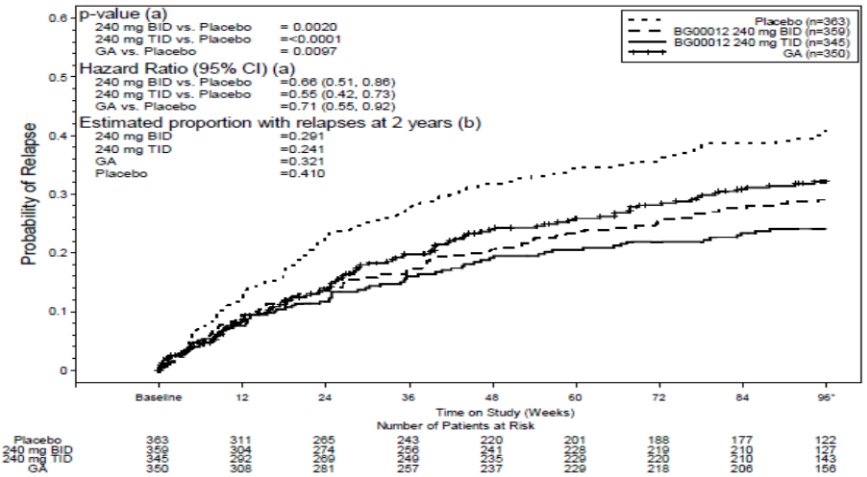
NOTE 1: Numbers in parentheses are percentages.
2: Observed data after subjects switched to alternative MS medications are excluded. Missing data prior to alternative MS medications and visits after subjects switched to alternative MS medications are included and imputed using the constant rate assumption.
(a) Percentage reduction, 95% CI and p-value for comparison between the active and placebo groups, based on negative binomial regression, adjusted for region and baseline volume of T1 lesions. NS: P-value <= 0.050 that is not considered statistically significant due to the applicable closed testing procedure.

Table 17. Summary of Proportion of Subjects Relapsed (INEC-Confirmed Relapses) at 2 Years

	Placebo	BG00012 240 mg BID	BG00012 240 mg TID	GA
Number of subjects in ITT population	363 (100)	359 (100)	345 (100)	350 (100)
Number of subjects relapsed				
Yes	140 (39)	93 (26)	76 (22)	104 (30)
No (Censored) (a)	223 (61)	266 (74)	269 (78)	246 (70)
Estimated proportion (b) of subjects relapsed at				
0 weeks	0.000	0.000	0.000	0.000
12 weeks	0.122	0.095	0.075	0.085
24 weeks	0.231	0.135	0.117	0.139
36 weeks	0.275	0.174	0.160	0.198
48 weeks	0.318	0.206	0.191	0.239
60 weeks	0.346	0.236	0.205	0.259
72 weeks	0.360	0.256	0.219	0.281
84 weeks	0.387	0.277	0.233	0.308
96 weeks minus 5 days (c)	0.401	0.291	0.241	0.321
96 weeks (2 years)	0.410	0.291	0.241	0.321
Number of subjects at risk (b)				
0 weeks	363	359	345	350
12 weeks	311	304	292	308
24 weeks	265	274	269	281
36 weeks	243	256	249	257
48 weeks	220	241	235	237
60 weeks	201	228	229	229
72 weeks	188	219	220	218
84 weeks	177	210	210	206
96 weeks minus 5 days (c)	164	192	195	189
96 weeks	122	127	143	156
Time (weeks) to first relapse (b)				
10th percentile	9.00	14.00	16.71	15.86
25th percentile	29.86	71.71	NA	57.43
50th percentile (Median)	NA	NA	NA	NA
Hazard ratio (active/placebo) (95% CI) (d)		0.66 (0.51, 0.86)	0.55 (0.42, 0.73)	0.71 (0.55, 0.92)
Percentage reduction (active versus placebo) (95% CI) (d)		34.0 (14.1, 49.3)	44.6 (26.6, 58.1)	28.6 (7.8, 44.6)
p-value (compared to placebo) (d)		0.0020	<0.0001	0.0097

NOTE 1: Only relapses confirmed by the INEC are included in the analysis.
2: Subjects who did not experience a relapse prior to switching to alternative MS medications or withdrew from study are censored at the time of switch/withdrawal.
(a) Subjects who did not have a relapse.
(b) Based on the Kaplan-Meier product limit method, up to 96 weeks.
(c) Earlier window of Week 96 visit.
(d) Based on Cox proportion hazards model, adjusted for baseline EDSS (<=2.0 vs >2.0), baseline age (<40 vs >=40), region and number of relapses in the 1 year prior to study entry.
Abbreviations: NA = not available since the proportion of subjects relapsed within the 2-year follow-up is less than the specified percentage. NS = comparison with p-value <= 0.050 that is not considered statistically significant due to the applicable closed testing procedure.

Figure 7. Time to First Relapse (INEC-Confirmed Relapses) - ITT Population



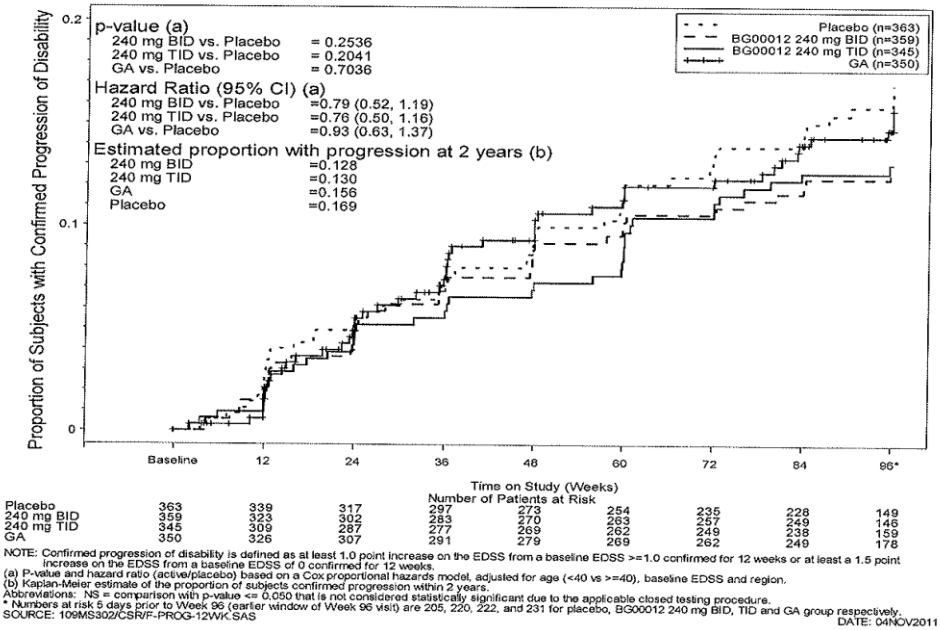
NOTE: Only relapses confirmed by the INEC are included in the analysis.
(a) P-value and hazard ratio (active/placebo) are based on Cox proportional hazards model, adjusted for baseline EDSS (<=2.0 vs >2.0), baseline age (<40 vs >=40), region, and number of relapses in the 1 year prior to study entry.
(b) Kaplan-Meier estimate of the proportion of subjects relapsed within 2 years.
Abbreviations: NS = comparison with p-value <= 0.050 that is not considered statistically significant due to the applicable closed testing procedure.
* Numbers at risk 5 days prior to Week 96 (earlier window of Week 96 visit) are 164, 192, 195, and 189 for placebo, BG00012 240 mg BID, TID and GA group respectively.

Table 18. Summary of Time to Confirmed Progression of Disability at 2 Years as Measured by Increase in EDSS score (12 Weeks Confirmation) with 109MS303 EDSS score data as of 25 October 2011

	Placebo	BG00012 240 mg BID	BG00012 240 mg TID	GA
Number of subjects in ITT population	363	359	345	350
Number of subjects in ITT population for EDSS (a)	363 (100)	359 (100)	345 (100)	350 (100)
Number of subjects progressed	52 (14)	40 (11)	38 (11)	48 (14)
Time (weeks) to progression (b)				
10th percentile	57.4	60.1	61.0	48.1
25th percentile	NA	NA	NA	NA
50th percentile	NA	NA	NA	NA
Estimated proportion of subjects with progression at 2-years (b)	0.169	0.128	0.130	0.156
Hazard ratio (active/placebo) (95% CI) (c)		0.79 (0.52, 1.19)	0.76 (0.50, 1.16)	0.93 (0.63, 1.37)
Percentage reduction (active versus placebo) (95% CI) (c)		21.4 (-18.8, 47.9)	23.8 (-15.9, 49.8)	7.3 (-37.2, 37.4)
p-value (compared to placebo) (c)		0.2536	0.2041	0.7036

NOTE 1: Confirmed progression of disability is defined as at least a 1.0 point increase on the EDSS from a baseline EDSS >=1.0 confirmed for 12 weeks or at least a 1.5 point increase on the EDSS from a baseline EDSS of 0 confirmed for 12 weeks.
2: Subjects are censored if they withdrew from study or switched to alternative MS medication without a progression.
3: Numbers in parentheses are percentages.
(a) Number of subjects in the ITT population with a baseline EDSS value.
(b) Estimated proportion of patients with progression and time to progression up to 96 weeks based on the Kaplan-Meier product limit method.
(c) Based on Cox proportion hazards model, adjusted for baseline EDSS, region and baseline age (<40 versus >=40).
Abbreviations: NA = not available since the proportion of subjects progressed within the 2-year follow-up is less than the specified percentage. NS = P-value <= 0.050 that is not considered statistically significant due to the applicable closed testing procedure.

Figure 8. Time to Confirmed Progression of Disability (12 Weeks Confirmation) as Measured by Increase in EDSS score - ITT Population



NOTE: Confirmed progression of disability is defined as at least 1.0 point increase on the EDSS from a baseline EDSS >=1.0 confirmed for 12 weeks or at least a 1.5 point increase on the EDSS from a baseline EDSS of 0 confirmed for 12 weeks.
(a) P-value and hazard ratio (active/placebo) based on a Cox proportional hazards model, adjusted for age (<40 vs >=40), baseline EDSS and region.
(b) Kaplan-Meier estimate of the proportion of subjects confirmed progression within 2 years.
Abbreviations: NS = comparison with p-value <= 0.050 that is not considered statistically significant due to the applicable closed testing procedure.
* Numbers at risk 5 days prior to Week 96 (earlier window of Week 96 visit) are 205, 220, 222, and 231 for placebo, BG00012 240 mg BID, TID and GA group respectively.
SOURCE: 109MS302/CSR/F-PROG-12WK.SAS
DATE: 04NOV2011

Tertiary outcome measures

The adjusted annualized rates of INEC-confirmed relapses at 1 year (0.462 in the placebo group, compared with 0.262 in the BG00012 BID group and 0.250 in the BG00012 TID group), represented reductions of 43.3% (p=0.0002) and 46% (p <0.0001) over placebo following 1 year of treatment with BG00012 BID and BG00012 TID, respectively. In the GA group, the annualized

relapse rate at 1 year (0.339) represented a significant reduction of 26.6% (p = 0.0298) compared to placebo.

Proportion of subjects relapsed over the first year was 31.8% in the placebo group, compared with 20.6% in the BG00012 BID group and 19.1% in the TID group. These data represent reductions in the risk of relapse at 1 year of 36.8% (p=0.0030) and 42.5% (p=0.0006), respectively, in the BG00012 BID and TID groups compared to placebo. The proportion of subjects with an INEC-confirmed relapse in the GA group (23.9%) was also lower than that of the placebo group and represented a significant (p=0.0217) reduction of 28.7% over placebo.

A total of 191 required IV steroid therapy in the placebo group, compared with 110 relapses in the BG00012 BID group and 95 in the BG0002 TID group. The adjusted annualized rate of relapses requiring IV steroids at 2 years was 0.344 in the placebo group, compared with 0.194 and 0.176 in the BG00012 BID and TID groups respectively and 0.256 in the GA group. The rate ratios versus placebo were 0.56 for BG00012 BID (p=0.0002), 0.51 for BG00012 TID (p<0.0001) and 0.74 for GA (p=0.0404).

The adjusted annualized rate of MS-related hospitalization (ie relapses or other MS-related complications) at 2 years was 0.055 in the placebo group, compared with 0.038 and 0.028 in the BG00012 BID and TID groups and 0.032 in GA groups respectively. These results corresponded to reductions of 32% (p=0.1092),50% (p=0.0098) and 43% (p=0.0282) respectively, over placebo.

At 2 years, improvement on MSFC composite z-score and individual components (PASAT 3, 9HPT, T25FW) and visual functions were observed for both BG00012 BID and TID groups however all the results were not statistically significant. Similar conclusions were made for the VAS, SF-36 -PCS component, EQ- 5D scores.

Consistency with the clinical findings was also observed on the MRI tertiary endpoints, although all of these results were not statistically significant. Positive findings were also observed in the patient health reported outcomes. In the GA group, similar findings were noted on the MRI and quality of life outcomes used in the efficacy analysis.

2.5.2.4. Ancillary analyses

The applicant presented a number of subgroup analyses, based on the following main criteria: gender, age, EDSS baseline score, volume of T2 lesions, number of Gd enhancing lesions, previous MS treatment; reason to discontinue prior approved MS treatments (lack of efficacy, other reasons or no prior approved treatment), number of relapses in the year prior to study entry (≤1 and ≥2), duration of illness. However, the subgroups as defined by the applicant provided limited information in relation to patients with high disease activity based on combination of clinical and MRI findings.

Therefore, the CHMP specifically requested the applicant to provide data on patients with high disease activity including the following subgroups: 1) patients having had at least 1 relapse in the previous year while on therapy, and having at least 9 T2- hyperintense lesions in cranial MRI or at least 1 Gd-enhancing lesion or 2) patients having an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year.

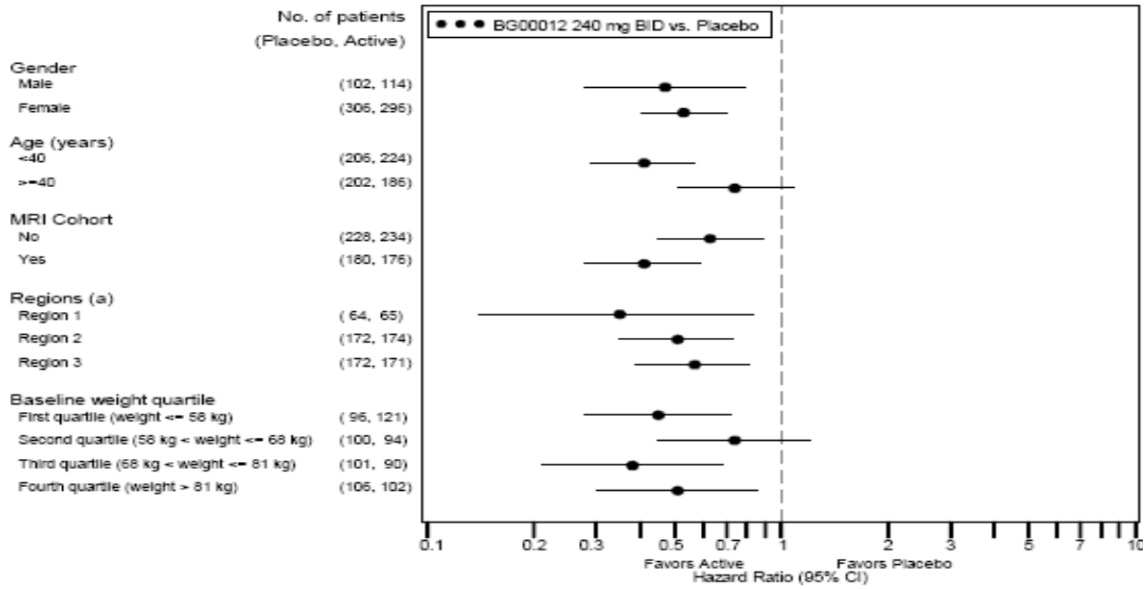
Main results are presented below.

Effect on relapses

Study 109MS301

Results are presented in Figures 9-11.

Figures 9-10. Proportion of subjects relapsed at 2 years by baseline data



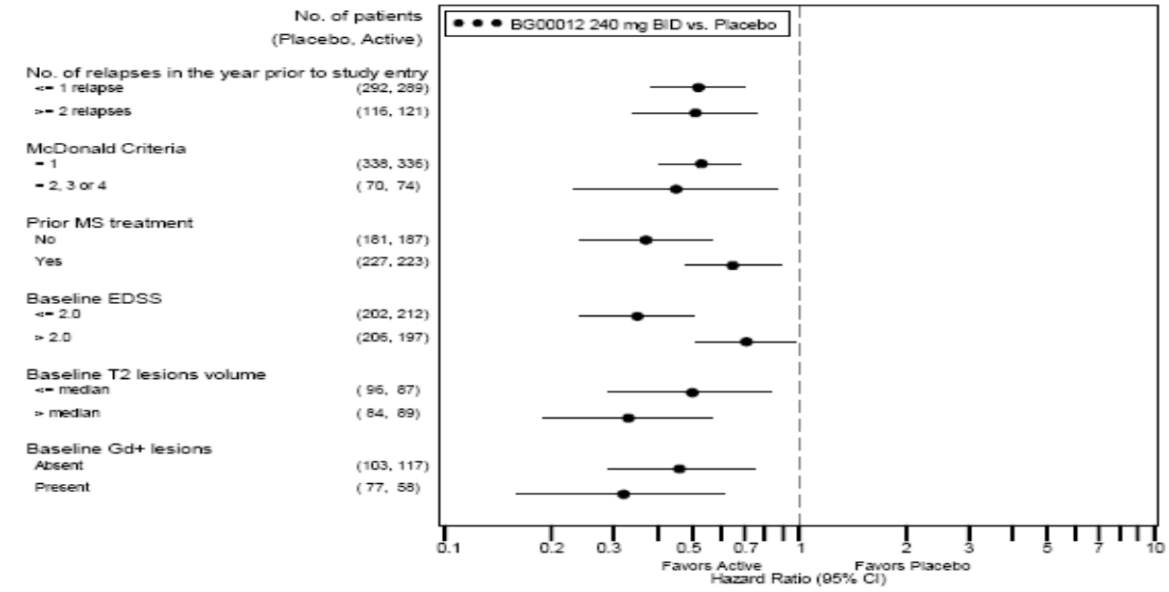
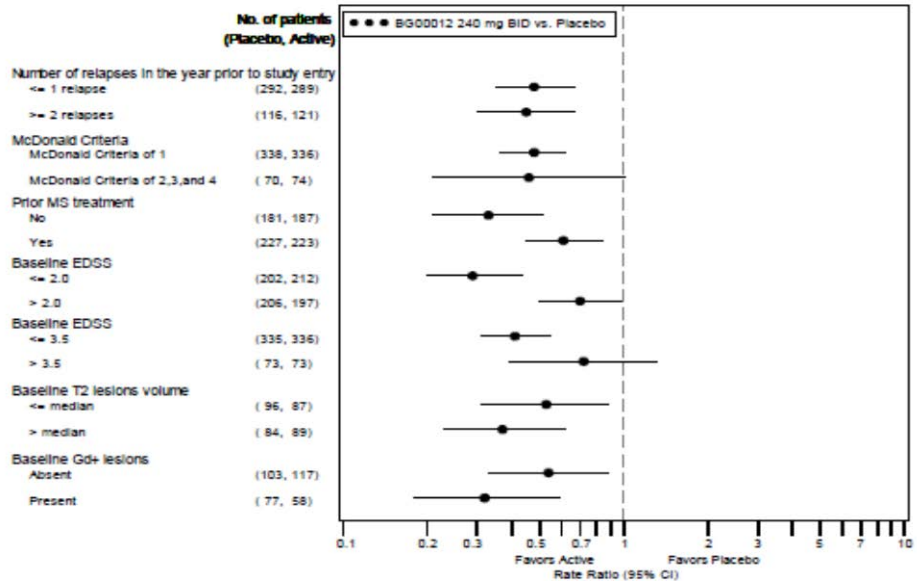


Figure 11. Annualized Relapse Rate (INEC Confirmed Relapses) at 2 years by baseline data



Study 109MS302

Results are presented in Figures 12-13.

Figure 12. Annualized relapse rate (INEC confirmed relapses) at 2 years by baseline data

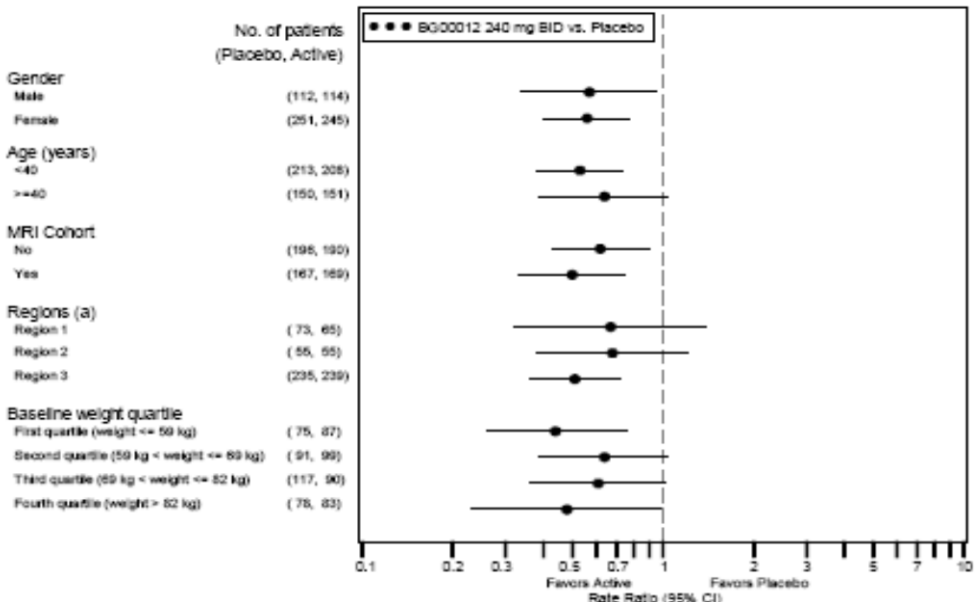
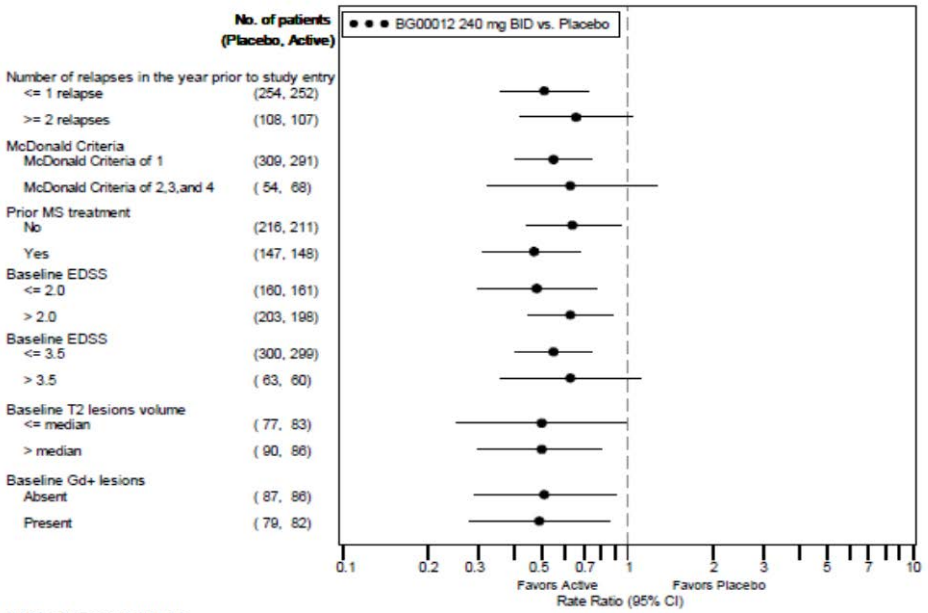


Figure 13. Annualized Relapse Rate (INEC Confirmed Relapses) at 2 years by baseline data



NOTE 1: Data source: MAA data.
2: Rate ratio (active/placebo) and (95% CI) based on negative binomial regression model. In general, the model adjusted for baseline EDSS (<=2.0 vs >2.0), baseline age (<40 vs >=40), region and number of relapses in the 1 year prior to study entry, except for the subgroup factor of interest.
SOURCE: BG12MS/EU/07232012/E15-F-ARR-FOREST-BS-302.SAS DATE: 01AUG2012

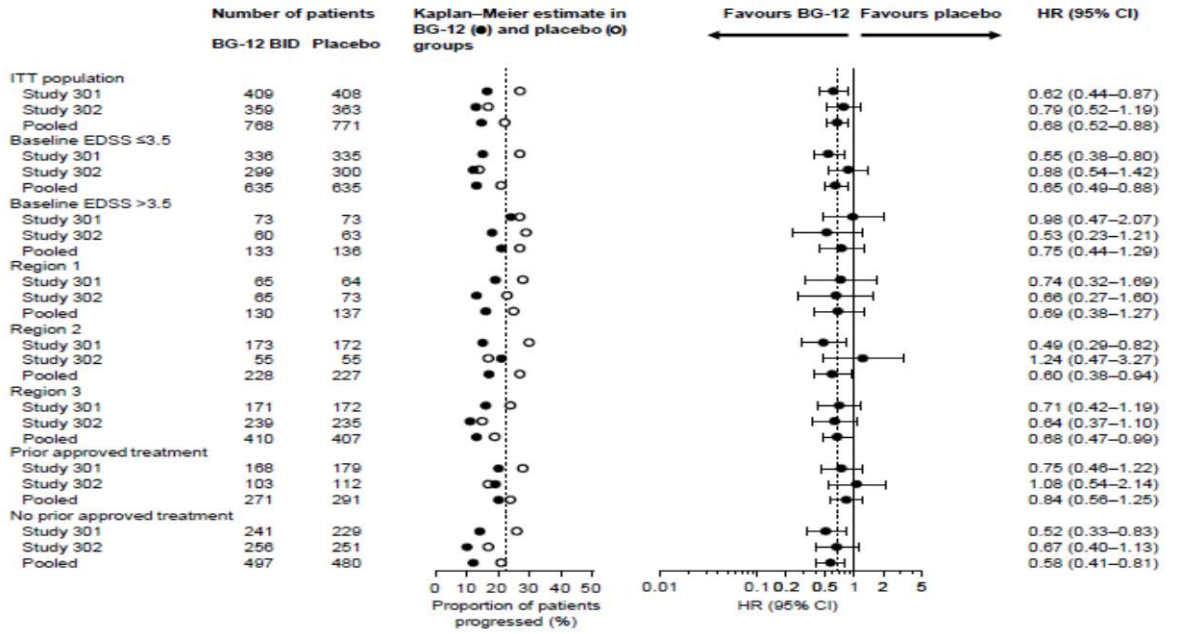
Effect on disability progression

Results by selected baseline characteristics are presented in Figures 14 and 17. Treatment group estimates for placebo and BG00012 are shown on the left panel, with a vertical reference line indicating the pooled placebo point estimate in the primary analysis. Hazard ratios (BG00012 versus placebo) with 95% confidence intervals (based on Cox proportional hazards model adjusted for baseline age (<40 vs ≥40), region, and baseline EDSS score, except for the subgroup factor of interest) are shown on the right panel, with a dashed vertical reference line indicating the pooled hazard ratio in the primary analysis. In the pooled analysis, study is included as a stratifying variable in the model.

Time to confirmed 12-week disability progression

Results are presented in Figure 14.

Figure 14. 12-week endpoint: BG00012 240mg BID vs. placebo



Source: Analyses of time to confirmed 12-week disability progression for BG-12 BID versus placebo by select baseline characteristics: Studies 301, 302 and pooled studies

Time to confirmed 24-week disability progression

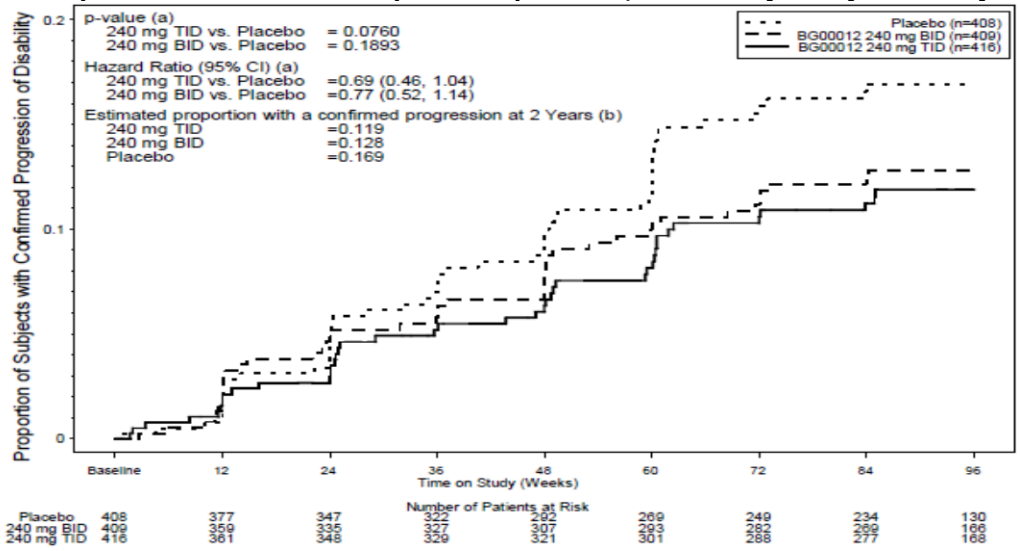
Results are presented in Tables 19-20 and Figures 15-17.

Table 19. Time to Confirmed Progression of Disability at 2 Years as Measured by Increase in EDSS score (24-Week Confirmation) , ITT Population, sensitivity analysis- study 109MS301

	Placebo	BG00012 240 mg BID	BG00012 240 mg TID
Number of subjects in ITT population	408	410	416
Number of subjects in ITT population for EDSS (a)	408 (100)	409 (100)	416 (100)
Number of subjects progressed	57 (14)	44 (11)	41 (10)
Time (weeks) to progression (b)			
10th percentile	48.4	60.0	62.4
25th percentile	NA	NA	NA
50th percentile	NA	NA	NA
Estimated proportion of subjects with progression at 2-years (b)	0.169	0.128	0.119
Hazard ratio (active/placebo) (95% CI) (c)		0.77 (0.52, 1.14)	0.69 (0.46, 1.04)
p-value (compared to placebo) (c)		0.1893	0.0760

NOTE 1: Confirmed progression of disability is defined as at least a 1.0 point increase on the EDSS from a baseline EDSS >=1.0 confirmed for 24 weeks or at least a 1.5 point increase on the EDSS from a baseline EDSS of 0 confirmed for 24 weeks.
2: Subjects are censored if they withdrew from study or switched to alternative MS medication without a progression.
3: Numbers in parentheses are percentages.
(a) Number of subjects in the ITT population with a baseline EDSS value.
(b) Estimated proportion of patients with progression and time to progression up to 96 week based on the Kaplan-Meier product limit method.
(c) Based on Cox proportion hazards model, adjusted for baseline EDSS, region and baseline age (<40 vs >=40).
Abbreviations: NA = not available since the proportion of subjects progressed within the 2-year follow-up is less than the specified percentage. NS = P-value <= 0.05 that is not considered statistically significant due to the closed testing procedure.

Figure 15. Time to Confirmed Progression of Disability as Measured by Increase in EDSS score (24-Week Confirmation)- ITT Population, sensitivity analysis- study 109MS301



NOTE: Confirmed progression of disability is defined as at least 1.0 point increase on the EDSS from a baseline EDSS >=1.0 confirmed for 24 weeks or at least a 1.5 point increase on the EDSS from a baseline EDSS of 0 confirmed for 24 weeks.
(a) P-value and hazard ratio (active/placebo) based on a Cox proportional hazards model, adjusted for age (<40 vs >=40), baseline EDSS and region.
(b) Kaplan-Meier estimate of the proportion of subjects confirmed progression within 2 years.

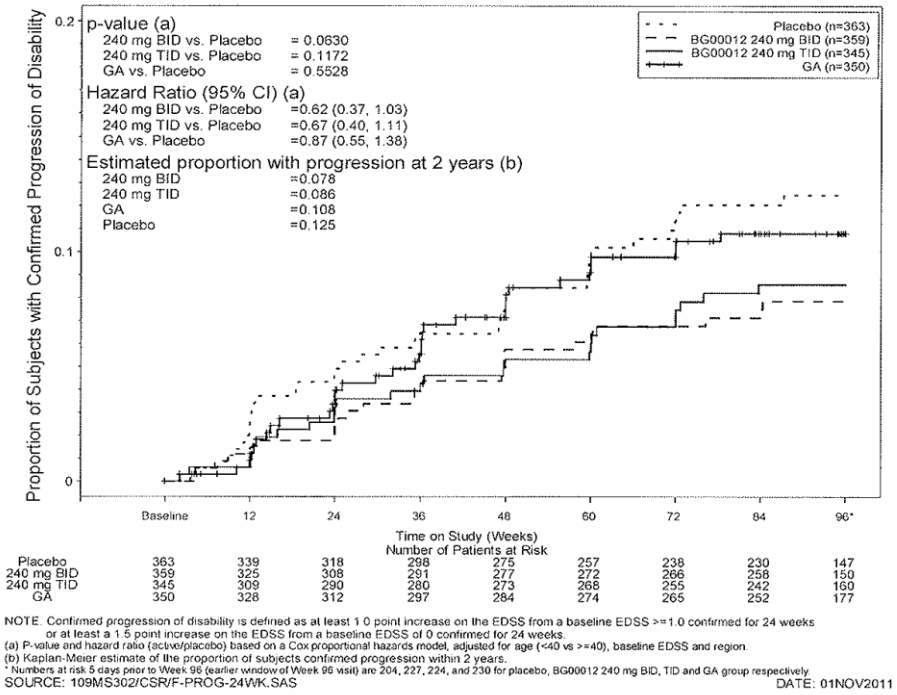
Table 20. Time to Confirmed Progression of Disability at 2 Years as Measured by Increase in EDSS score (24-Week Confirmation)– ITT Population, sensitivity analysis- study 109MS302

	Placebo	BG00012 240 mg BID	BG00012 240 mg TID	GA
Number of subjects in ITT population	363	359	345	350
Number of subjects in ITT population for EDSS (a)	363 (100)	359 (100)	345 (100)	350 (100)
Number of subjects progressed	39 (11)	24 (7)	25 (7)	34 (10)
Time (weeks) to progression (b)				
10th percentile	60.1	NA	NA	72.1
25th percentile	NA	NA	NA	NA
50th percentile	NA	NA	NA	NA
Estimated proportion of subjects with progression at 2-years (b)	0.125	0.078	0.086	0.108
Hazard ratio (active/placebo) (95% CI) (c)		0.62 (0.37, 1.03)	0.67 (0.40, 1.11)	0.87 (0.55, 1.38)
Percentage reduction (active versus placebo) (95% CI) (c)		38.3 (-2.7, 62.9)	33.1 (-10.6, 59.5)	13.0 (-37.8, 45.1)
p-value (compared to placebo) (c)		0.0630	0.1172	0.5528

NOTE 1: Confirmed progression of disability is defined as at least a 1.0 point increase on the EDSS from a baseline EDSS >=1.0 confirmed for 24 weeks or at least a 1.5 point increase on the EDSS from a baseline EDSS of 0 confirmed for 24 weeks.
2: Subjects are censored if they withdrew from study or switched to alternative MS medication without a progression.
3: Numbers in parentheses are percentages.
(a) Number of subjects in the ITT population with a baseline EDSS value.
(b) Estimated proportion of patients with progression and time to progression up to 96 week based on the Kaplan-Meier product limit method.
(c) Based on Cox proportion hazards model, adjusted for baseline EDSS, region and baseline age (<40 vs >= 40).
Abbreviations: NA = not available since the proportion of subjects progressed within the 2-year follow-up is less than the specified percentage. NS = P-value <= 0.05 that is not considered statistically significant due to the applicable closed testing procedure.

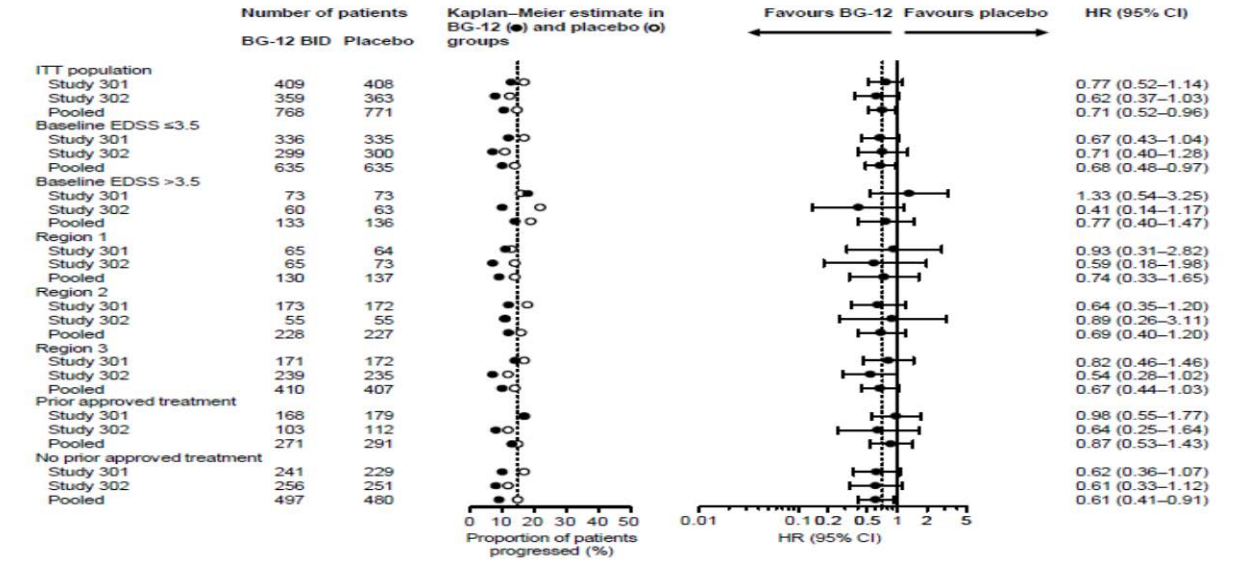
SOURCE: 109MS302/CSR/T-PROG-24WK.SAS DATE: 28OCT2011

Figure 16. Time to Confirmed Progression of Disability as Measured by Increase in EDSS (24-Week Confirmation)- ITT Population, sensitivity analysis- study 109MS302



NOTE: Confirmed progression of disability is defined as at least 1.0 point increase on the EDSS from a baseline EDSS >=1.0 confirmed for 24 weeks or at least a 1.5 point increase on the EDSS from a baseline EDSS of 0 confirmed for 24 weeks.
(a) P-value and hazard ratio (active/placebo) based on a Cox proportional hazards model, adjusted for age (<40 vs >=40), baseline EDSS and region.
(b) Kaplan-Meier estimate of the proportion of subjects confirmed progression within 2 years.
* Numbers at risk 5 days prior to Week 96 (earlier window of Week 96 visit) are 204, 227, 224, and 230 for placebo, BG00012 240 mg BID, TID and GA group respectively.
SOURCE: 109MS302/CSR/F-PROG-24WK.SAS DATE: 01NOV2011

Figure 17. 24-week endpoint: BG00012 240mg BID vs. placebo

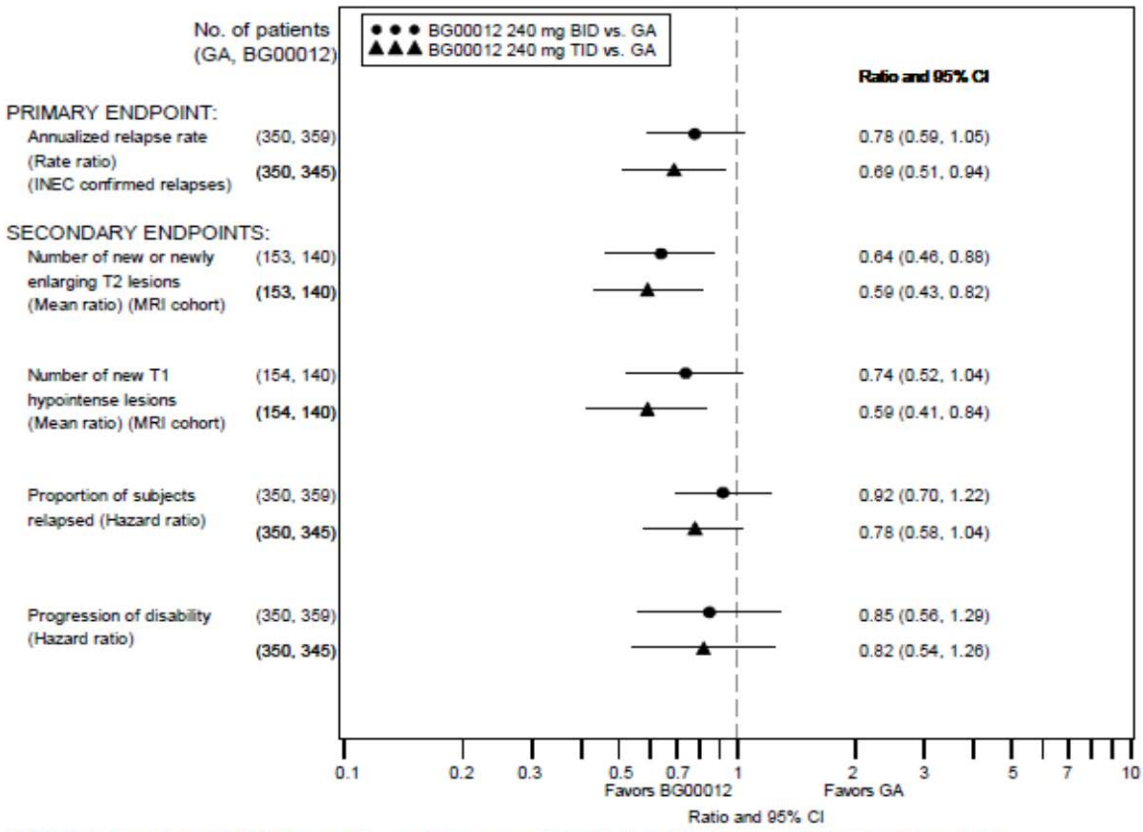


Source: Analyses of time to confirmed 24-week disability progression for BG-12 BID versus placebo by select baseline characteristics: Studies 301, 302 and pooled studies

Comparison versus Glatiramer

This is presented in Figure 18.

Figure 18



NOTE: Analysis models for BG00012 versus GA comparisons are described within the individual primary analysis tables of the endpoints.

Patients with high disease activity

As there is no consensus concerning the definition of high disease activity in RMS patients, the applicant presented a number of subgroup analyses. Results are presented in Table 21.

Table 21. Efficacy in patients with high disease activity as defined by the applicant

	Placebo (pooled)	BID (pooled)	Ratio (95% CI) BID vs placebo
≥1 relapse in prior year, recent prior treatment ≥12 months and Gd+; OR naïve ≥ 2 relapses in prior year and Gd+ (n=90, 6% BG00012 BID population)*			
ARR	0.56	0.23	0.42 (0.21,0.83)
Number of New/Newly Enlarging T2 lesions	29.1	6.9	0.23 (0.14, 0.37)
Disability Progression (12-week confirmed)	0.44	0.24	0.66 (0.29,1.50)
Modified Rio Score			0.25 (0.09,0.66)
IFN for ≥12 months AND:			
≥1 relapse on IFN and ≥9 T2 lesions or Gd+ OR unchanged or increased relapse rate (n=318, 20% BG00012 BID population)*			
ARR	0.36	0.20	0.57 (0.39, 0.84)
Number of New/Newly Enlarging T2 lesions	17.0	4.3	0.15 (0.08,0.28)
Disability Progression (12-week confirmed)	0.16	0.18	1.19 (0.66,2.15)
Modified Rio Score			0.16 (0.07,0.37)
≥1 relapse in prior year and recent prior treatment ≥12 months; OR naïve and ≥2 relapses in prior year (n=494,			

32% BG00012 BID population)			
ARR	0.44	0.24	0.54 (0.40,0.74)
Number of New/Newly Enlarging T2 lesions	16.9	4.8	0.27 (0.18,0.41)
Disability Progression (12-week confirmed)	0.25	0.17	0.73 (0.48,1.11)
Modified Rio Score			0.34 (0.18,0.63)
≥2 relapses in prior year and Gd+ (n=93, 6% BG00012 BID population)			
ARR	0.58	0.23	0.40 (0.22,0.71)
Number of New/Newly Enlarging T2 lesions	32.8	8.2	0.22 (0.13, 0.36)
Disability Progression (12-week confirmed)	0.33	0.26	1.11 (0.47,2.60)
Modified Rio Score			0.16 (0.06,0.41)
≥1 relapse in prior year and EDSS ≥2.5 (n=782, 50% BG00012 BID population)**			
ARR	0.41	0.27	0.66 (0.52, 0.84)
Number of New/Newly Enlarging T2 lesions	15.8	4.6	0.24 (0.16, 0.35)
Disability Progression (12-week confirmed)	0.21	0.15	0.72 (0.50, 1.04)
Modified Rio Score			0.38 (0.23,0.63)
≥2 relapses in prior year and EDSS ≥2.5 (n=236, 15% BG00012 BID population)***			
ARR	0.62	0.36	0.59 (0.40,0.86)
Number of New/Newly Enlarging T2 lesions	18.6	5.6	0.27 (0.14,0.49)
Disability Progression (12-week confirmed)	0.26	0.16	0.62 (0.33,1.15)
Modified Rio Score			0.45 (0.19,1.08)
≥ 3 relapses in prior year (n=71, 5% BG00012 BID population)			
ARR	0.67	0.41	0.60 (0.30, 1.20)
Number of New/Newly Enlarging T2 lesions	24.6	10.3	0.33 (0.12,0.94)
Disability Progression (12-week confirmed)	0.39	0.36	0.81 (0.33,1.97)
Modified Rio Score			NA
≥ 4 relapses in prior 3 years (n=243, 17% BG00012 BID population)			
ARR	0.52	0.28	0.55 (0.37, 0.80)
Number of New/Newly Enlarging T2 lesions	19.0	7.5	0.31 (0.17, 0.57)
Disability Progression (12-week confirmed)	0.30	0.17	0.60(0.33,1.08)
Modified Rio Score			0.30 (0.12,0.70)

Notes: 1) Adjusted relapse rate and rate ratio based on negative binomial regression, 2) Unadjusted mean number of lesions, rate ratio based on negative binomial regression;3) Disability Progression (12-week confirmed) based on Kaplan Meier estimates, HR based on Cox proportional hazards model, 4) Modified Rio Score based on ordinal logistic regression, *: Tysabri and Gilenya SmPCs, except that for study 109MS301/109MS302, unchanged or increased relapse rate refers to the 1 year prior to study entry compared to the 2 years before that, **: Gilenya EPAR, ***:Coyle PK. *J Neurol.* 2008

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 22. Summary of efficacy for trial 109MS301

Title: A randomized, multicenter, double-blind, placebo-controlled, dose-comparison study to determine the efficacy and safety of BG00012 in subjects with RRMS			
Study identifier	**109MS301**		
Design	randomized, multicenter, parallel-group, double-blind, rater-blind, placebo-controlled. Subjects were randomized in a 1:1:1 ratio to BG00012 240 mg twice daily (BID), BG00012 240 mg 3 times daily (TID), or placebo.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		96 weeks (additional 4 week follow up for subjects who do not enrol into the extension study, 109MS303) Not applicable Not applicable (separate extension study: Study 109MS303)
Hypothesis	Superiority		
Treatments groups	Placebo		taken orally 3 times a day Treatment duration: 96 week; randomized: N = 410
	BG00012 240 mg BID		taken orally 2 BG00012 capsules (120 mg each) twice a day and 2 placebo capsules once a day (after a starting dose of 1 BG00012 capsule twice a day and 1 placebo capsule once a day for 7 days) Treatment duration of 96 weeks; randomized: N = 411
	BG00012 240 mg TID		taken orally 2 BG00012 capsules (120 mg each) 3 times a day (after a starting dose of 1 BG00012 capsule 3 times a day for 7 days) Treatment duration of 96 weeks; randomized: N = 416
Endpoints and definitions	Primary endpoint	Proportion of subjects relapsed	Proportion of subjects who experienced a protocol-defined relapse at 2 years, confirmed by the blinded Independent Neurology Evaluation Committee [INEC].
	clinically relevant Secondary endpoints	Annualized relapse rate (ARR)	Number of protocol-defined relapses per year over 2 years, confirmed by the blinded INEC.
		Time to confirmed (12-week) disability progression	Progression of disability as measured by a ≥ 1.0 point increase on the EDSS from a baseline EDSS score ≥1.0 that was confirmed at least 12 weeks later, or a ≥ 1.5 point increase on the EDSS from a baseline EDSS score = 0 that was confirmed at least 12 weeks later. A progression could start but could not be confirmed when a subject was experiencing an INEC-confirmed relapse.
	Other Relevant endpoints	Time to confirmed (24-week) disability progression	Progression of disability as measured by a ≥ 1.0 point increase on the EDSS from a baseline EDSS score ≥1.0 that was confirmed at least 24 weeks later, or a ≥ 1.5 point increase on the EDSS from a baseline EDSS score = 0 that was confirmed at least 24 weeks later. A progression could start but could not be confirmed when a subject was experiencing an INEC-confirmed relapse.
Database lock	01 April 2011		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat (for clinical endpoints) at 2 years			
Descriptive statistics and estimate variability	**Treatment group**	**Placebo**	**BG00012 240 mg BID**	**BG00012 240 mg TID**
	Number of subjects	408	410	416
	Proportion of subjects relapsed[3]	0.461	0.270	0.260
	ARR (adjusted) [4]	0.364	0.172	0.189
	95% CI	(0.303, 0.436)	(0.138, 0.214)	(0.153, 0.234)
	Proportion of subjects with confirmed (12 week) disability progression[3]	0.271	0.164	0.177

Effect estimate per comparison	Primary endpoint: Proportion of subjects relapsed[5]	**Comparison groups**	**BG00012 240 mg BID versus Placebo**
		Hazard ratio	0.51
		95% CI	(0.40, 0.66)
		p-value	<0.0001
		Comparison groups	**BG00012 240 mg TID versus Placebo**
		Hazard ratio	0.50
		95% CI	(0.39, 0.65)
		p-value	<0.0001
	Secondary endpoint: ARR[4]	**Comparison groups**	**BG00012 240 mg BID versus Placebo**
		Rate ratio	0.473
		95% CI	(0.365, 0.613)
		p-value	<0.0001
		Comparison groups	**BG00012 240 mg TID versus Placebo**
		Rate ratio	0.521
		95% CI	(0.404, 0.670)
		p-value	<0.0001
	Secondary endpoint: Time to confirmed (12-week) disability progression[5]	**Comparison groups**	**BG00012 240 mg BID versus Placebo**
		Hazard ratio	0.62
		95% CI	(0.44, 0.87)
		p-value	0.0050
		Comparison groups	**BG00012 240 mg TID versus Placebo**
		Hazard ratio	0.66
		95% CI	(0.48, 0.92)
		p-value	0.0128
Analysis description	**Sensitivity Analysis**		
Analysis population and time point description	Intent to treat (for clinical endpoints) at 2 years		

Descriptive statistics and estimate variability	**Treatment group**	**Placebo**	**BG00012 240 mg BID**	**BG00012 240 mg TID**
	Number of subjects	408	410	416
	Proportion of subjects with confirmed (24 week) disability progression[3]	0.169	0.128	0.119
Effect estimate per comparison	Time to confirmed (24-week) disability progression	**Comparison groups**		**BG00012 240 mg BID versus Placebo**
		Hazard ratio		0.77
		95% CI		(0.52, 1.14)
		p-value		0.1893
		Comparison groups		**BG00012 240 mg TID versus Placebo**
		Hazard ratio		0.69
		95% CI		(0.46, 1.04)
		p-value		0.0760
Notes	[3] Kaplan-Meier estimate, [4] Based on negative binomial regression, [5] Based on Cox proportional hazards model, [6] Based on ordinal logistic regression			

Table 23. Summary of efficacy for trial 109MS302

Title: A randomized, multicenter, placebo-controlled and active reference (Glatiramer Acetate) comparison study to evaluate the efficacy and safety of BG00012 in subjects with RRMS			
Study identifier	**109MS302**		
Design	randomized, multicenter, parallel-group, placebo-controlled, active reference (glatiramer acetate [GA]) comparator, double-blind (BG00012/placebo), rater-blind study. Subjects were randomized in a 1:1:1:1 ratio to BG00012 240 mg BID, BG00012 240 mg TID, or placebo, or GA.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		96 weeks (additional 4 weeks follow up for subjects who do not enrol into the extension study, 109MS303) Not applicable Not applicable (separate extension study: study 109MS303)
Hypothesis	Superiority (for each active treatment group versus placebo)		
Treatments groups	Placebo		taken orally 3 times a day (after a starting dose of 1 matching placebo capsule 3 times a day for 7 days) Treatment duration: 96 weeks; randomized: N = 363
	BG00012 240 mg BID		taken orally 2 BG00012 capsules (120 mg each) twice a day and 2 placebo capsules once a day (after a starting dose of 1 BG00012 capsule twice a day and 1 placebo capsule once a day for 7 days) Treatment duration: 96 weeks; randomized: N = 362
	BG00012 240 mg TID		taken orally 2 BG00012 capsules (120 mg each) 3 times a day (after a starting dose of 1 BG00012 capsule 3 times a day for 7 days) Treatment duration: 96 weeks; randomized: N = 345
	GA		20 mg subcutaneous injection, once daily. Treatment duration: 96 weeks; randomized: N = 360
Endpoints and definitions	Primary endpoint	Annualized relapse rate (ARR)	Number of protocol-defined relapses per year over 2 years, confirmed by the blinded INEC.
	clinically relevant Secondary endpoints	Proportion of subjects relapsed	Proportion of subjects who experienced a protocol-defined relapse at 2 years, confirmed by the INEC.
		Time to confirmed (12-week) disability progression	Progression of disability as measured by a ≥ 1.0 point increase on the EDSS from a baseline EDSS score ≥1.0 that was confirmed at least 12 weeks later, or a ≥ 1.5 point increase on the EDSS from a baseline EDSS score = 0 that was confirmed at least 12 weeks later. A progression could start but could not be confirmed when a subject was experiencing an INEC-confirmed relapse.

	Other Relevant endpoints	Time to confirmed (24-week) disability progression	Progression of disability as measured by a ≥ 1.0 point increase on the EDSS from a baseline EDSS score ≥1.0 that was confirmed at least 24 weeks later, or a ≥ 1.5 point increase on the EDSS from a baseline EDSS score = 0 that was confirmed at least 24 weeks later. A progression could start but could not be confirmed when a subject was experiencing an INEC-confirmed relapse.
Database lock	06 October 2011		

Results and Analysis

Analysis description	**Primary Analysis**				
Analysis population and time point description	Intent to treat (for clinical endpoints) at 2 years				
Descriptive statistics and estimate variability	**Treatment group**	**Placebo**	**BG00012 240 mg BID**	**BG00012 240 mg TID**	**GA**
	Number of subjects	363	359	345	350
	ARR (adjusted) [3]	0.401	0.224	0.198	0.286
	95% CI	(0.329, 0.488)	(0.179, 0.282)	(0.156, 0.252)	(0.232, 0.353)
	Proportion of subjects relapsed[4]	0.410	0.291	0.241	0.321
	Proportion of subjects with confirmed (12 week) disability progression[4]	0.169	0.128	0.130	0.156

Effect estimate per comparison	Primary endpoint: ARR[3]	**Comparison groups**	**BG00012 240 mg BID versus Placebo**
		Rate ratio	0.560
		95% CI	(0.423, 0.740)
		p-value	<0.0001
		Comparison groups	**BG00012 240 mg TID versus Placebo**
		Rate ratio	0.495
		95% CI	(0.369, 0.662)
		p-value	<0.0001
		Comparison groups	**GA versus Placebo**
		Rate ratio	0.714
		95% CI	(0.548, 0.931)
		p-value	0.0128
	Secondary endpoint: Proportion of subjects relapsed[5]	**Comparison groups**	**BG00012 240 mg BID versus Placebo**
		Hazard ratio	0.66
		95% CI	(0.51, 0.86)
		p-value	0.0020
		Comparison groups	**BG00012 240 mg TID versus Placebo**
		Hazard ratio	0.55
		95% CI	(0.42, 0.73)
		p-value	<0.0001
		Comparison groups	**GA versus Placebo**
		Hazard ratio	0.71

		95% CI	(0.55, 0.92)
		p-value	0.0097
	Secondary endpoint: Time to confirmed (12-week) disability progression[5]	**Comparison groups**	**BG00012 240 mg BID versus Placebo**
		Hazard ratio	0.79
		95% CI	(0.52, 1.19)
		p-value	0.2536
		Comparison groups	**BG00012 240 mg TID versus Placebo**
		Hazard ratio	0.76
		95% CI	(0.50, 1.16)
		p-value	0.2041
		Comparison groups	**GA versus Placebo**
		Hazard ratio	0.93
		95% CI	(0.63, 1.37)
		p-value	0.7036
Analysis description	**Sensitivity Analysis**		
Analysis population and time point description	Intent to treat (for clinical endpoints) at 2 years		

	Treatment group	**Placebo**	**BG00012 240 mg BID**	**BG00012 240 mg TID**	**GA**
	Number of subjects	363	359	345	350
	Proportion of subjects with confirmed (24 week) disability progression[4]	0.125	0.078	0.086	0.108

	Secondary endpoint: Time to confirmed (24-week) disability progression[5]	**Comparison groups**	**BG00012 240 mg BID versus Placebo**
		Hazard ratio	0.62
		95% CI	(0.37,1.03)
		p-value	0.063
		Comparison groups	**BG00012 240 mg TID versus Placebo**
		Hazard ratio	0.67
		95% CI	(0.40,1.11)
		p-value	0.1172
		Comparison groups	**GA versus Placebo**
		Hazard ratio	0.87
		95% CI	(0.55,1.38)
		p-value	0.5528
Notes	[3] Kaplan-Meier estimate, [4] Based on negative binomial regression, [5] Based on Cox proportional hazards model, [6] Based on ordinal logistic regression		

2.5.2.5. Analysis performed across trials (pooled analyses and meta-analysis)

The applicant presented an integrated analysis of data from studies 109MS301 and 109MS302.

Main Results

Effect on relapses

The risk of relapse at 2 years was reduced by 42.5% (p <0.0001) and 47.4% (p <0.0001) following treatment with BG00012 BID and TID, respectively, compared with placebo. Both 240 mg BID and TID reduced the ARR by 48.5% compared to placebo over 2 years of treatment.

Effect on disability progression

For BG00012 BID and TID groups respectively, 32% and 30% reductions in the risk of 12-week confirmed progression were observed (p=0.0034 and p<0.0059) and 29% and 32% reductions in the risk of 24-week confirmed progression were also noted (p=0.0278 and p=0.0177).

Maintenance of the effect

Consistent statistically significant effects with both doses of BG00012 of similar direction and magnitude were seen across the studies at each 6-month period. The percentage reduction and 95% CI in the annualized relapse rate by 6-month interval for BG00012 BID compared to placebo are presented in Table 24.

Table 24. ARR by 6-month interval for BG00012 BID compared to placebo

	Study 109MS301	Study 109MS302	Pooled data
0-6 months	43% (18, 61)	43% (19, 59)	43% (27, 56)
6-12 months	55% (31, 70)	40% (5, 62)	49% (31, 63)
12-18 months	52% (24, 70)	32% (-16, 60)	45% (22, 61)
18-24 months	50% (19, 70)	33% (-15, 61)	44% (20, 61)

Withdrawal/Rebound effect

For subjects who completed Studies 109MS301 and 109MS302 and chose not to enroll into Study 109MS303, there was a 1 month follow-up period post-dose. This analysis included data for subjects who prematurely discontinued study treatment and were followed for at least 1 day, and subjects who completed the 2-year study treatment period, and with at least 1 day off treatment (safety follow-up after the last dose, or gap between parent and extension study).

Of the 1044 subjects included in this analysis, 58%, 54%, and 55% of subjects had up to 1 month of follow-up data, and 42%, 46%, and 45% had greater than 1 month follow-up data in the placebo, BG00012 BID, and BG00012 TID groups, respectively. The total number of subject-years of follow-up in this analysis was approximately 52, 67, and 60 in the placebo, BG00012 BID, and BG00012 TID groups, respectively. Based on the analysis, the adjusted annualized relapse rate for subjects following the last dose was 0.178 (95% CI: 0.094, 0.338) in the placebo group, compared with 0.119 (95% CI: 0.061, 0.233) in the BG00012 BID group and 0.210 (95% CI: 0.118, 0.373) in the BG00012 TID group.

2.5.2.6. Clinical studies in special populations

No trials have been performed in any special MS patient populations.

2.5.2.7. Supportive study

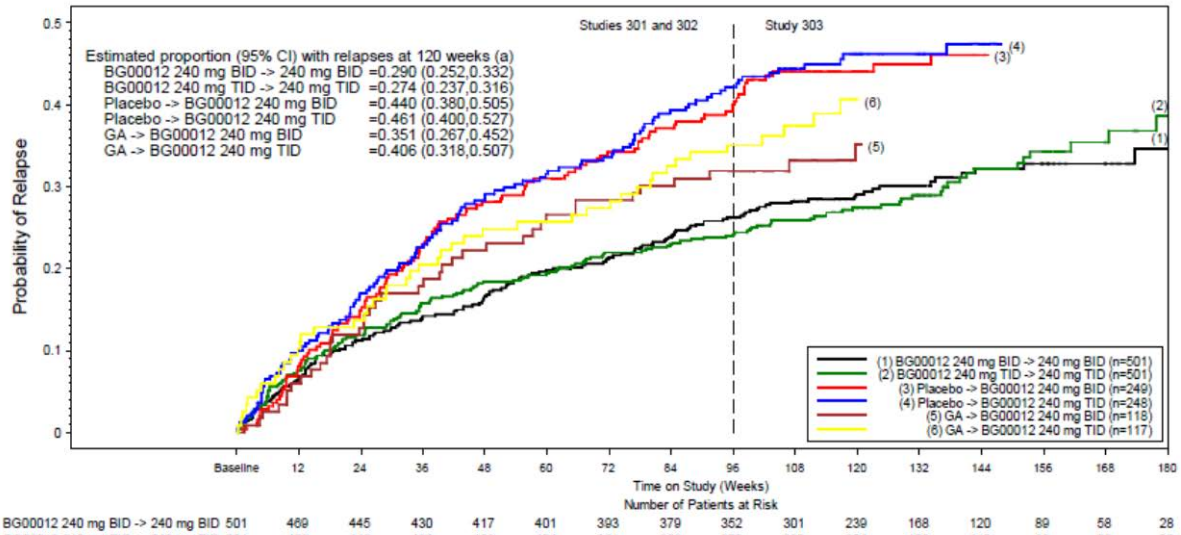
Study 109MS303 is an ongoing, 5 year, multicenter, parallel-group, randomized, dose-blind, rater-blind, dose-comparison extension study designed to evaluate the long-term safety and efficacy of 2 dose regimens of BG00012 in subjects with RRMS. Subjects who were randomized to BG00012 in studies 109MS301 or 109MS302 continue on the same BG00012 dose to which they were originally randomized. Subjects who were randomized to placebo or to GA (Study 109MS302) were re-randomized in a 1:1 ratio to BG00012 240 mg BID or 240 mg TID.

The primary objective was to evaluate the long-term safety profile of BG00012. Efficacy endpoints included annualized relapse rate, proportion of subjects relapsed, disability progression as measured by the EDSS, and MRI measures of disease activity in subjects at selected investigational sites based on the availability of the necessary MRI equipment (MRI cohort).

Available data as of 03 August 2011 were submitted as part of the present application. A total of 1738 subjects had entered the study and 1734 subjects who had received a dose of BG00012 240 mg BID or TID as of this date, were analysed.

Main results are presented in Figures 19 and 20.

Figure 19. Time to First Relapse (Objective Relapses) – Study 109MS303 ITT Population (Studies 109MS301 and 109MS302 and Study 109MS303 Data Combined)

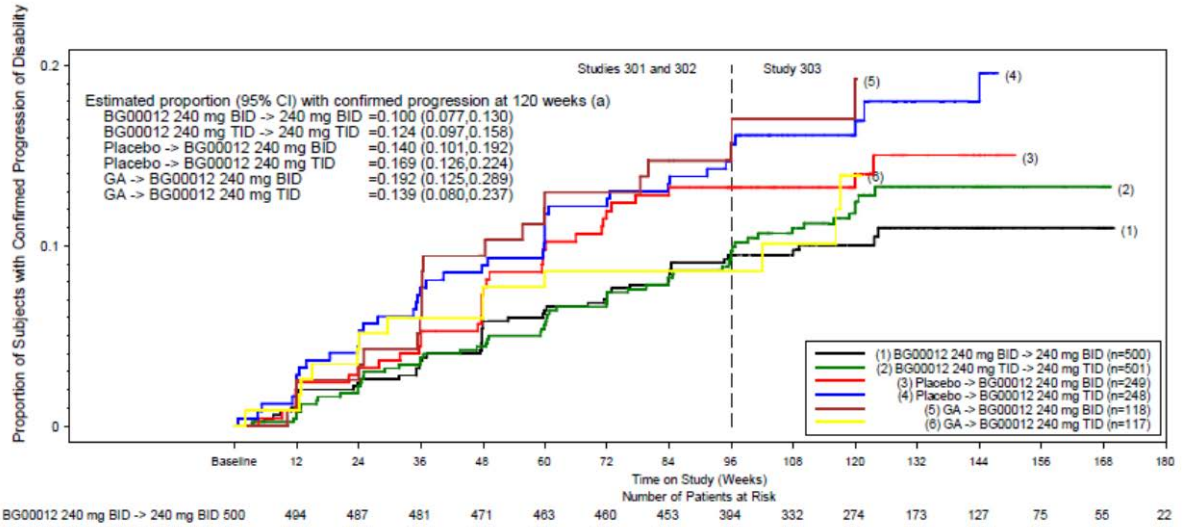


Number of Patients at Risk

BG00012 240 mg BID -> 240 mg BID	501	469	445	430	417	401	393	379	352	301	239	168	120	89	58	28
BG00012 240 mg TID -> 240 mg TID	501	463	442	422	409	404	391	386	372	322	251	170	113	89	50	29
Placebo -> BG00012 240 mg BID	249	229	212	192	179	171	161	154	142	106	78	54	41	26	20	5
Placebo -> BG00012 240 mg TID	248	223	206	192	177	168	163	149	139	105	77	58	40	28	17	8
GA -> BG00012 240 mg BID	118	111	103	95	89	84	81	79	73	47	33	25	18	15	11	2
GA -> BG00012 240 mg TID	117	105	101	93	88	87	85	79	74	47	31	18	14	11	8	3

NOTE 1: Only objective relapses are included in the analysis.
2: Subjects who did not experience a relapse prior to switching to alternative MS medications or withdrawal from study are censored at the time of switch/withdrawal.
3: Kaplan-Meier estimate is not calculated if the number of subjects at risk is less than 30.
(a) Kaplan-Meier estimate.

Figure 20. Time to Confirmed Progression of Disability as Measured by Increase in EDSS score (24-Week Confirmation) – Study 109MS303 ITT Population (Studies 109MS301 and 109MS302 and Study 109MS303 Data Combined)



Number of Patients at Risk

BG00012 240 mg BID -> 240 mg BID	500	494	487	481	471	463	460	453	394	332	274	173	127	75	55	22
BG00012 240 mg TID -> 240 mg TID	501	497	489	483	478	471	464	456	410	332	282	170	132	71	53	21
Placebo -> BG00012 240 mg BID	249	244	241	236	226	214	206	203	182	138	115	71	52	30	22	5
Placebo -> BG00012 240 mg TID	248	241	236	229	223	219	213	208	186	127	106	62	53	29	20	8
GA -> BG00012 240 mg BID	118	116	114	109	104	100	99	97	83	46	38	20	18	12	8	1
GA -> BG00012 240 mg TID	117	116	112	109	109	107	105	103	90	54	41	21	18	12	8	2

NOTE 1: Confirmed progression of disability is defined as at least a 1.0 point increase on the EDSS from a baseline EDSS >= 1.0 confirmed for 24 weeks or at least a 1.5 point increase on the EDSS from a baseline EDSS of 0 confirmed for 24 weeks.
2: Subjects are censored if they withdrew from study or switched to alternative MS medication without a progression.
3: Kaplan-Meier estimate is not calculated if the number of subjects at risk is less than 30.
(a) Kaplan-Meier estimate.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical development programme consisted of one phase II placebo controlled study (Study C-1900) and two phase III studies, one placebo controlled (Study 109MS301) and one placebo and active controlled (Study 109MS302). However the latter study including the active comparator (glatiramer acetate: GA) was not designed for a comparison of treatment effects in BG00012 in relation to GA. In addition interim data from an ongoing extension study of the 2 phase III studies (Study 109MS303) were provided.

In the dose-ranging study, patients received BG00012 120 mg per day, 360 mg per day or 720 mg per day for 24 weeks. In study 109MS301 and study 109MS302, two different doses of BG00012 were used: 240 mg BID and 240 mg TID.

The duration of the completed studies, 6 month double blind treatment phase in the dose ranging study and 2 years in the pivotal studies, were considered adequate by the CHMP.

All studies were multicentre and multinational and included only patients with relapsing-remitting MS. Diagnosis of MS was based on the McDonald criteria. Inclusion and exclusion criteria were similar across these 4 studies, patients with a history of treatment with glatiramer were excluded in study 109MS302. Patients over 55 years were also excluded from the clinical studies. Of note, baseline EDSS score above 5.5 was defined as an exclusion criterion and the clinical characteristic for disease activity was the number of relapses in the last year, “at least one relapse within the 12 months prior to randomization”, that was used as inclusion criterion.

Relevant efficacy endpoints were selected in accordance with the guideline on Clinical Investigation of Medicinal Products for the Treatment of Multiple Sclerosis or MS GL (CPMP/EWP/561/98 Rev. 1).

An Independent Neurology Evaluation Committee (INEC) was established to re-assess relapses that were already defined by the examining neurologist. The conclusion of the INEC was used for the definition of the confirmed relapses. From the CHMP viewpoint, this was not considered as a conventional procedure. However, a sensitivity analysis based on objective relapses (those determined by the site and not by INEC) was also performed and seen as highly relevant as it assigned a status of relapse that is commonly used in recent MS trials.

Time to disability progression was measured by at least a 1.0 point increase on the EDSS from baseline EDSS score ≥ 1.0 that was confirmed 12 weeks later, or at least a 1.5 point increase on the EDSS from baseline EDSS score equal to 0 that was confirmed 12 weeks later. Hence the six-month sustained disability progression endpoint, as recommended in the MS GL (CPMP/EWP/561/98 Rev. 1) was chosen only for the sensitivity analysis on this endpoint.

Data from studies 109MS301 and 109MS302 were also pooled for analysing a number of efficacy outcome measures including ARR at 2 years, risks of 12-week and 24 week confirmed progression. According to the applicant, this integrated analysis was pre-specified. However, the CHMP was of the opinion that the pooled analysis could not be regarded as pre-specified, given its date of inclusion in the final SAP. Results of study MS301 were also already available before the SAP for the pooled analysis was performed. In addition, the CHMP considered that there were a number of differences between the two pivotal studies that questioned the value of pooling of the data, especially with regard to the endpoints, time to 3-and 6- months sustained disability progression. These included the following: 1) approximately 40 % of the patients were recruited in Region 3 for study 109MS301 when it was 65% for study 109MS302, 2) EDSS scores were on average higher in study 109MS302, 3) 40% of patients had prior MS treatment in study 109MS301 against 29% in

study 109MS302, 4) The number of volume of Gd-enhancing and T2 lesions was higher in study 109MS302 and 5) The criterion for discontinuation of study medication after 48 weeks was different in the two studies. Differences in the 2 pivotal studies regarding the effect for 12-week confirmed disability progression were also observed in all groups including the placebo (see below). It appeared that no consistency between the two studies could be seen for those patients with baseline EDSS score greater than 3.5 for either the 12-week or the 24-week endpoints (see Figures 14-17). Rules for switching medication were not the same as well, this being recognised by the applicant itself to potentially impact on disability progression at 24 week endpoint.

Across studies 109MS301 and 109MS302, patients were aged between 18 and 55 (median 38-39 years) and were mainly Caucasian. Approximately 70% were female. The mean baseline EDSS score was 2.5. Only a small number of patients had a score of 3.5 or above. 40% of patients had prior MS treatment in study 109MS301, only 29% in study 109MS302. In both pivotal studies, there was a clear low relapse rate in the placebo group. Most of the patients in all treatment groups experienced 0 relapses (109MS301: 58% placebo, 76% BG00012 240 mg BID, 77% BG00012 240 mg TID; 109MS302: 61% placebo, 74% BG00012 240 mg BID, 78% BG00012 240 mg TID, 70% GA).

Efficacy data and additional analyses

Dosing rationale

In the dose ranging study (C-1900) using either 120 mg QD BG00012 (120 mg), 120 mg TID BG00012 (360 mg), 240 mg TID BG00012 (720 mg), the highest dose, 240 mg TID of BG00012 showed statistically significant differences in comparison to placebo for the primary endpoint, the total number of new Gd-enhancing lesions over 4 scans at different weeks and all secondary MRI endpoints. There was a clear difference in efficacy between the BG00012 240 mg TID dose group compared to the 120 mg QD and the 120 mg TID treatment groups as both of these lower doses did not demonstrate any significant effect in the EE population when compared to placebo for any MRI endpoints. However, considerable imbalances at baseline for the mean number of Gd-enhancing lesions across the groups, notably in the 120 mg TID group which presented patients with higher disease activity ie higher number of Gd-enhancing lesions were observed and additional sensitivity analyses were requested to further interpret the MRI results. In these analyses using the number of baseline Gd-enhancing lesions as covariates, BG00012 120 mg TID also provided statistically significant results for the primary endpoint (p=0.009). The mean total number of Gd-enhancing lesions was 1.7 and 1.1 for the 120 mg TID and the 240 mg TID treatment arm, respectively. Results were supported by analyses on various MRI endpoints. However, the CHMP noted that this lower dose (120 mg TID) was no longer tested in the phase III studies. Dosing regimens of 240 mg BID and TID were subsequently used and were considered acceptable by the CHMP in view of the overall results.

In phase III studies, there was a small difference between the two doses altogether for the efficacy on relapses (although the differences were higher in study 109MS302), the selection of 240 mg BID as the recommended dose was therefore considered acceptable by the CHMP. In addition, all of these studies were based on a 1 week escalation regimen and dose reductions were allowed to minimise the flushing and GI events. The CHMP hence accepted to use such flexibility in dosing regimen for the final posology as the tolerability profile was also found adequate.

Effect on relapses

In study 109MS301, BG00012 BID and TID reduced the risk of relapse at 2 years over placebo by 49% (p <0.0001) and 50% (p <0.0001), respectively. The annualized relapse rate versus placebo was also reduced by 53% (p <0.0001) and 48% (p <0.0001), respectively. In the sensitivity analyses, results were consistent with the primary analysis showing statistically significant differences for both active treatment groups in comparison to placebo. Based on the analysis using

"objective relapses", consistent results were observed for the lower BG00012 dose (BG00012 240 mg BID : HR=0.5; BG00012 240 mg TID: HR=0.54).

In study 109MS302, BG00012 BID and TID reduced the risk of relapse at 2 years over placebo by 34% (p=0.0020) and 45% (p <0.0001), respectively; the annualized relapse rate versus placebo was reduced by 44% (p <0.0001) and 50.5% (p<0.0001), respectively. When using analysis based on "objective relapses", the reduction over placebo in the annualized rate of objective relapse at 2 years was similar to that for INEC-confirmed relapses and was 40.8% and 51.5%, for BG00012 BID and BG00012 TID, respectively (p <0.0001 for both tested doses). In the GA group, the ARR was also significantly lower than the placebo group, with a reduction of 28.6% compared to placebo (p=0.0128) at 2 years.

For both pivotal studies, a lesser effect of BG00012 on relapses in patients with higher EDSS score at baseline, in non-naïve patients consistently in patients aged 40 years and above (see Figures 9-13) was seen.

Effect on disability progression

In study 109MS301, both DMF tested doses reached statistical significance when compared to placebo in reducing the risk of 12-week sustained disability progression (240 mg BID: p=0.0050, 240 mg TID: p=0.0128). The hazard ratios were 0.62 and 0.66 for 240 mg BID and 240 mg TID groups, respectively. In study 109MS302, both DMF tested doses failed to reach statistical significance when compared to placebo in reducing the risk of 12-week sustained disability progression (240 mg BID: p=0.2536; 240 mg TID: p=0.2041). The hazard ratios were 0.79 and 0.76 for 240 mg BID and 240 mg TID groups, respectively. In both individual studies, a sensitivity analysis was performed in terms of 24-week sustained disability progression. Although, none of the BG00012 treatment arms reached statistical significance when compared to placebo, a similar trend as for 12 weeks confirmed disability progression was however noted. In study 109MS301, the hazard ratios were 0.77 and 0.69 for 240 mg BID and 240 mg TID groups, respectively. In study 109MS302, the hazard ratios were 0.62 and 0.67 for 240 mg BID and 240 mg TID groups, respectively.

The effect on disability progression was not considered robust enough to support a claim for a disease-modifying drug taking into account that the pooled analysis could not be accepted for methodological reasons and that the other additional analyses provided by the applicant were of post-hoc nature.

Comparison versus Glatiramer and indirect comparison with other treatments

Comparative data were provided of treatment effects in BG00012 in relation to GA. In the majority of the primary and secondary endpoints, including the ARR and time to 3 month sustained disability, an effect in favour of BG00012 was observed (see Figure 18). The CHMP concluded that no confirmatory conclusions could be drawn from these data since this analysis was a post-hoc direct comparison.

Based on historical comparisons, there was a relative reduction for ARR of 44-53% under BG00012 compared to a relative reduction in ARR of around 30% for interferons and GA, suggesting at least comparable efficacy on relapses for BG00012 when compared to approved first-line treatment. However, second-line treatments provided even better results on this endpoint. When considering time to disability progression, results for BG00012 are less convincing. No confirmatory conclusions could be made regarding relative efficacy versus approved MS products, however the CHMP considered these data supportive of the efficacy in the broad RRMS population.

Long-term efficacy and withdrawal after discontinuation

In study 109MS303, efficacy was maintained after one year in patients previously treated by BG00012 (Figures 19-20). A positive effect was seen in patients previously receiving placebo. The study is currently ongoing and the CHMP therefore recommended to further investigate this issue once more data become available.

Efficacy data in patients who discontinued study drug were considered limited to evaluate a possible rebound effect.

Patients with high disease activity

With respect to the definition of the high disease activity "patients having at least one relapse in the past year while on therapy with beta-interferon, and at least 9 T2- hyperintense lesions in cranial MRI or at least 1 Gd-enhancing lesion or having an unchanged or increased relapse rate" (20 % BG00012 BID population, n=177 in DEFINE and n=141 in CONFIRM); and "patients with at least 2 relapses in past year and 1 Gd lesion at baseline" (6% BG00012 BID population, n=42 in DEFINE and n=51 in CONFIRM) used by the applicant, the CHMP considered that it was analogous to the currently authorised indications for Tysabri and Gilenya. Although a general consensus over the definition of high disease activity is currently lacking, these subgroups were considered relevant. Reference to treatment effects in these subgroups was considered essential to the prescribing physician and was thus included in section 5.1 of the SmPC.

Extrapolation of the efficacy to Relapsing Multiple Sclerosis (RMS)

The CHMP requested the applicant to further investigate whether an extrapolation of the study data could be envisaged to the RMS population, taking into account mechanistic considerations and available literature. Only patients with RRMS were included in the main clinical trials, however, subgroups of patients defined as "representative of SMPS patients" by the applicant were analysed. The CHMP however did not consider these subgroup analyses adequate, especially taking into account that the sensitivity of the EDSS measurement is known to be reduced in the higher range. Literature data suggested that there is a pathophysiological difference described for RRMS and SPMS with superimposed relapses as the process in SPMS relates more to a cellular/axon loss than to simple inflammation. Given the DMF mechanism on MS is not completely understood and in the absence of trial data in SPMS patients, the CHMP concluded that a clear extrapolation of efficacy observed in RRMS patients to SPMS patients with superimposed relapses cannot be made.

Additional expert consultation

At the SAG Neurology meeting held on 13 February 2013, the applicant proposed indication under discussion was as follows:

"TECFIDERA is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (see section 5.1)."

The main SAG conclusions for DMF were as follows:

- The efficacy over placebo on disease activity (relapse and MRI parameters) was demonstrated. However, efficacy over progression of disability was not considered as clearly established, in particular as the effect lacked consistency across the two studies and as both studies failed on the time to 6 month sustained disability secondary endpoint.

- Although only historical comparison can be made across products in the absence of head to head comparative data, the panel felt that the efficacy of DMF is comparable to that of interferon beta.

- The risks, some of them serious (e.g. decrease of lymphocyte counts, elevation of hepatic enzymes) are manageable with adequate risk minimisation measures. As efficacy data are lacking for patients with high disease activity, the panel considered that DMF could be a valuable alternative to interferon beta for the treatment of patients with mildly active RRMS.

Having considered the SAG conclusions and that the efficacy of DMF over the broad RRMS population was evident in several subgroups of patients (including those defined as high disease activity), the CHMP recommended an unrestricted RRMS indication. A cross reference was also recommended to "important information on the population for which efficacy has been established" that has been included in section 5.1 of the SmPC.

2.5.4. Conclusions on the clinical efficacy

The CHMP concluded that efficacy was demonstrated in patients with relapsing-remitting multiple sclerosis in the proposed dosing regimen for Tecfidera (DMF).

2.6. Clinical safety

The safety database presented in this dossier included the following datasets: 1) placebo-controlled MS studies (C-1900, Part 1; 109MS301; 109MS302) referred to as Pool A and 2) placebo-controlled and uncontrolled MS clinical studies (C-1900, 109MS301, 109MS302, 109MS303) or referred to as Pool B.

In addition to these studies, data on the psoriasis safety experience with DMF together with three other fumaric salts that are currently marketed in this indication in Germany were provided using the following datasets: 1) short term placebo-controlled studies with BG00012 in psoriasis (Study 12/01 Part 1, 12-Week and Study 01/02, 16-Week) or referred to as Pool C and 2) controlled psoriasis studies and their uncontrolled extensions (Study 12/01 Part 2 , 6 months and Study 03/03 , 2 years) referred to as Pool D.

2.6.1. Patient exposure

A total of 2560 patients suffering from MS have been exposed to BG00012 during the clinical study program (of which 92 subjects are not integrated in the safety database), receiving at least one dose of the study drug, and were evaluable for safety. Overall, this number of subjects accounts for around 3600 person-years of exposure. 1469 (1095) of 2560 subjects have been exposed for ≥1 year (≥2 years) at or above the dose, which the applicant applied for.

2.6.2. Adverse events

The AE profile for Pool A representing all placebo-controlled studies, is considered representative of the DMF safety profile in MS patients and included 3 dosing regimens (lower BG00012 doses including 120 mg QD and 120 mg TID, 240 mg BID, 240 mg TID) and placebo groups (see Table 25).

Table 25. Incidence of AEs at least 2% higher for any BG00012 group or GA relative to placebo (Pool A)

	Placebo	BG00012 Lower Doses	BG00012 240 mg BID	BG00012 240 mg TID	Total BG00012	GA
Number of subjects in safety population	836 (100)	128 (100)	769 (100)	823 (100)	1720 (100)	351 (100)
Number of subjects with an event	769 (92)	114 (89)	733 (95)	767 (93)	1614 (94)	304 (87)
FLUSHING	39 (5)	65 (51)	265 (34)	240 (29)	570 (33)	6 (2)
NASOPHARYNGITIS	169 (20)	13 (10)	170 (22)	179 (22)	362 (21)	51 (15)
DIARRHOEA	86 (10)	11 (9)	107 (14)	136 (17)	254 (15)	14 (4)
NAUSEA	72 (9)	10 (8)	93 (12)	115 (14)	218 (13)	16 (5)
URINARY TRACT INFECTION	96 (11)	4 (3)	107 (14)	95 (12)	206 (12)	46 (13)
UPPER RESPIRATORY TRACT INFECTION	88 (11)	5 (4)	99 (13)	101 (12)	205 (12)	27 (8)
FATIGUE	91 (11)	6 (5)	94 (12)	103 (13)	203 (12)	30 (9)
ABDOMINAL PAIN UPPER	47 (6)	9 (7)	76 (10)	94 (11)	179 (10)	4 (1)
PROTEINURIA	59 (7)	0	67 (9)	85 (10)	152 (9)	30 (9)
ABDOMINAL PAIN	37 (4)	4 (3)	73 (9)	69 (8)	146 (8)	5 (1)
PRURITUS	35 (4)	11 (9)	62 (8)	64 (8)	137 (8)	7 (2)
VOMITING	38 (5)	3 (2)	65 (8)	58 (7)	126 (7)	9 (3)
RASH	29 (3)	8 (6)	58 (8)	58 (7)	124 (7)	9 (3)
HOT FLUSH	16 (2)	6 (5)	52 (7)	55 (7)	113 (7)	5 (1)
ERYTHEMA	10 (1)	2 (2)	36 (5)	54 (7)	92 (5)	6 (2)
SINUSITIS	31 (4)	2 (2)	35 (5)	52 (6)	89 (5)	11 (3)
BRONCHITIS	32 (4)	3 (2)	35 (5)	49 (6)	87 (5)	16 (5)
ALBUMIN URINE PRESENT	27 (3)	0	46 (6)	36 (4)	82 (5)	18 (5)
DYSPEPSIA	23 (3)	3 (2)	35 (5)	42 (5)	80 (5)	6 (2)
MUSCLE SPASMS	35 (4)	1 (<1)	27 (4)	50 (6)	78 (5)	8 (2)
MICROALBUMINURIA	24 (3)	0	35 (5)	36 (4)	71 (4)	15 (4)
ASPARTATE AMINOTRANSFERASE INCREASED	18 (2)	2 (2)	33 (4)	32 (4)	67 (4)	14 (4)
GASTROINTESTINAL DISORDER	8 (<1)	3 (2)	18 (2)	34 (4)	55 (3)	2 (<1)
HYPERHIDROSIS	11 (1)	2 (2)	17 (2)	27 (3)	46 (3)	5 (1)
ABDOMINAL DISCOMFORT	13 (2)	6 (5)	19 (2)	15 (2)	40 (2)	1 (<1)
INFLUENZA LIKE ILLNESS	14 (2)	5 (4)	10 (1)	17 (2)	32 (2)	3 (<1)
VIRAL UPPER RESPIRATORY TRACT INFECTION	12 (1)	4 (3)	13 (2)	10 (1)	27 (2)	7 (2)
MUSCULOSKELETAL STIFFNESS	11 (1)	1 (<1)	7 (<1)	4 (<1)	12 (<1)	9 (3)
INJECTION SITE INDURATION	0	0	0	1 (<1)	1 (<1)	7 (2)
INJECTION SITE ERYTHEMA	0	0	0	0	0	31 (9)
INJECTION SITE MASS	0	0	0	0	0	7 (2)
INJECTION SITE PAIN	0	0	0	0	0	29 (8)
INJECTION SITE PRURITUS	0	0	0	0	0	13 (4)
INJECTION SITE SWELLING	0	0	0	0	0	10 (3)

NOTE 1: Numbers in parentheses are percentages.
2: Data from Studies 109MS301 and 109MS302 after subjects switched to alternative MS treatment are excluded.
3: A subject was counted only once within each preferred term.
4: Preferred terms are presented by decreasing order of incidence in Total BG00012 column.

Table 25 shows a clear excess of BG00012 over placebo for flushing and GI disorders related AEs.

Flushing related events

Flushing (including hot flush) and related symptoms, erythema, generalized erythema, burning sensation, skin burning, feeling hot, and hyperaemia occurred at a substantially increased incidence with BG00012 compared with placebo (Study 109MS301: 8% placebo, 50% BG00012 BID, 46% BG00012 TID; Study 109MS302: 9% placebo, 39% BG00012 BID, 34% BG00012 TID, 5% GA). In the majority of patients, flushing and related symptoms were non-serious in nature and were assessed as mild or moderate in severity. Severe flushing was reported in 1% of patients in both the BG00012 240mg BID and TID groups. More BG00012 than placebo treated patients discontinued due to flushing although the incidence was not high (Study 109MS301: <1% placebo, 2% BG00012 BID, 1% BG00012 TID; Study 109MS302: 0% placebo, 4% BG00012 BID, 2% BG00012TID, 0% GA).

In Pool A, the incidence of flushing and related event was highest during the first 3 months of the studies (6% placebo, 36% BG00012 BID and 35% BG00012 TID), then decreased substantially during the second 3 months (<1% placebo and 7% for both DMF groups), and continued to drop during the subsequent intervals through Month 24 (placebo: <1% to1%, BG00012BID: 2% to 6% and BG00012 TID: 2% to 4%).

Gastrointestinal related adverse events

GI related events were reported at an increased incidence with BG00012 compared with placebo (Study 109MS301: 36% placebo, 44% BG00012 BID, 45% BG00012 TID; Study 109MS302: 26% placebo, 36% BG00012 BID, 41% BG00012 TID, 15% GA). In the majority of patients, GI related events were non-serious in nature, and assessed as mild or moderate in severity. Among BG00012-treated patients there was an increased incidence of events in the GI SOC that led to treatment discontinuation compared with placebo (Study 109MS301: 1% placebo, 5% BG00012 BID, 6% BG00012 TID; Study 109MS302: <1% placebo, 3% BG00012 BID, 5% BG00012 TID, <1% GA), although the incidence of individual GI AEs including diarrhoea, nausea, vomiting, abdominal pain upper, and abdominal pain was not high (≤2% each event).

In Pool A, the incidence of events associated with GI tolerability (e.g., diarrhoea, nausea, upper abdominal pain, abdominal pain, vomiting, dyspepsia, gastroenteritis, GI disorder) in the BG00012 groups was highest during the first 3 months (18% versus 27% and 30%), then decreased substantially during the second 3-month interval (6% versus 7% and 8%) and occurred at a similar incidence during the subsequent 3-month intervals (4% to 6% versus 3% to 7% and 4% to 7%) through month 24.

Skin related events

In Pool A, the overall incidence of events in the skin and subcutaneous tissue disorders SOC was higher in the BG00012 groups compared with the placebo group (20% placebo vs. 32% BG00012 BID, 32% BG00012 TID, 17% GA). Pruritus (4% placebo vs. 8% BG00012 BID, 8% BG00012 TID, 2% GA), rash (3% vs. 8%, 7%, and 3%), erythema (1% vs. 5%, 7%, and 2%), and hyperhidrosis (1% vs. 2%, 3%, 1%) were among the events with an incidence of 2% or more in BG00012 treated subjects compared to placebo. In the BG00012 BID and TID groups, the incidence of events in the skin and subcutaneous disorders SOC was highest during the first 3 months of the studies (placebo: 10%, BG00012 BID: 19%, BG00012 TID: 20%, GA: 7%), then decreased during the second 3 months (placebo: 4%, BG00012 BID: 7%, BG00012 TID: 7%, GA: 4%), and continued to drop during the subsequent intervals through Month 24 (placebo: 2% to 4% , BG00012 BID: 2% to 7%, BG00012 TID: 3% to 5%, and GA: 2% to 3%).

Infections

Overall the incidence of infections reported as an adverse event was 56% for placebo (469 patients) and 60% for both BG00012 groups (463 patients for BID, 493 patients for TID).

Cardiac related events

Intensive monitoring for ischemic CV events was undertaken in the MS Phase 3 studies (109MS301 and 109MS302). CV history and/or risk factors were collected at baseline.

The incidences for cardiac disorder events were similar for all treatment groups (5% placebo, 5% BG00012 BID, 6% BG00012 TID, 5% GA). Same findings were noted for ischemic related events (cardiovascular ischemia: <1% placebo, 1% BG00012 BID, <1% BG00012 TID, 1% GA, cerebrovascular ischemia: 1 subject each in the placebo, BG00012 BID and GA group, 2 subjects in the BG00012 TID group). These subjects had two or more risk factors. ECG changes reported as adverse events were low in all treatment groups (<1%).

At the CHMP request, a pooled analysis using the pivotal studies (109MS301 and 109MS302) was provided to further investigate the risk of cardiovascular events under BG00012 treatment in relation to existing cardiovascular risk factors at baseline. Results showed no evidence for a higher risk in patients treated with BG00012, regardless of the dose administered. The overall numbers of

events were similar in all treatment and dosing groups except for a slightly higher AE rate for tachycardia and palpitations in patients with risk factors at baseline.

Hepatic related events

In Pool A, the incidence of hepatic adverse events was similar in all treatment groups (9% placebo vs. 9% BG00012 BID, 10% BG00012 TID, and 11% GA). However, in the BG00012 groups, elevations of liver transaminases were most frequently reported and of slightly higher incidence compared to placebo: ALT increased (5% placebo vs. 6% BG00012 BID and TID and GA each), AST increased (2% placebo vs. 4% BG00012 BID and TID and GA each), gamma-glutamyl transferase (gamma-GT) (2% placebo vs. 3% BG00012 BID, 2% BG00012 TID, 2% GA), and hepatic enzyme increased (1% placebo vs. <1% BG00012 BID, 1% BG00012 TID, 2% GA). Hepatic related events leading to treatment discontinuation were low (<1%) and similar in all groups.

Renal related events

In Pool A, incidences of renal and urinary related adverse events were slightly higher in BG00012-treated subjects compared to placebo (18% placebo vs. 19% BG00012 BID, 22% BG00012 TID, 17% GA). The most common AEs were: proteinuria (7% placebo, 9% BG00012 BID, 10% BG00012 TID, 9% GA), haematuria (4% placebo, 4% BG00012 BID, 5% BG00012 TID, 3% GA), and microalbuminuria (3% placebo, 5% BG00012 BID, 4% BG00012 TID, 4% GA). In the majority of subjects, the events were rated as mild or moderate in severity and related to dose. No increased treatment discontinuations in patients with AEs were noted (<1% in all groups). Of note, there were two subjects in the extension study 109MS303, who experienced a non-serious chronic renal failure. Laboratory tests for these two subjects did not reveal irregularities indicative for renal failure.

At the CHMP request, a pooled analysis separating the lower doses (BG00012 120 mg QD and 120 mg TID) was provided to further investigate renal and urinary toxicity by comparing these doses to 240 mg BID and 240 mg TID. A dose-relationship could not be confirmed for BG00012 treatment (0% to 22%) for BG00012 120 mg QD, 120 mg TID, 240 mg BID, and for 240 mg TID due to the high incidence of these events in the placebo group (18%). Although less AEs were reported in study C-1900 due to different renal monitoring, combined data from phase II and III studies (Pool A) appeared to suggest a dose-related reporting of renal and urinary AEs.

Malignancies

Placebo-controlled studies revealed a malignancy rate for BG00012 BID and TID similar to that of placebo and GA (<1% [3 subjects] placebo, <1% [2 subjects] BG00012 BID, <1% [2 subjects] BG00012 TID, 1% [4 subjects] GA). Malignancies included breast cancer, basal cell skin carcinoma, and breast neoplasm in the placebo group; transitional cell carcinoma of renal pelvis and basal cell skin carcinoma in the BG00012 BID group; breast cancer and cervix cancer in the BG00012 TID group; and cervix cancer, endometrial cancer, thyroid cancer, and basal cell skin carcinoma in the GA group.

In the uncontrolled extension studies, eight additional BG00012-treated subjects with malignancies were reported. Of those subjects, one was treated in study C-1900 for 11 months with BG00012 (breast cancer), 2 were treated for the first time with BG00012 in study 109MS303 (breast cancer in situ; rectal cancer), and 5 subjects received continued treatment with BG00012 in study 109MS303 (cutaneous malignant melanoma in two subjects; papillary renal cell carcinoma, squamous cell carcinoma of the lung, and salivary gland cancer in one subject each). For Pool B (controlled and uncontrolled studies), malignancies were reported in 0.4% of subjects from the BG00012 BID group and in 0.5% of subjects from the BG00012 TID group.

In the overall clinical MS program, there were 3 malignancies in placebo-treated subjects compared to 12 malignancies in BG00012-treated subjects and 4 malignancies in GA-treated subjects. Ten (10) of the 12 BG00012 malignancies were first reported after 12 months of being on BG00012 in the study.

Suicide and depression

In Pool A, these events (including depression, suicidal ideation, suicide attempt, completed suicide) occurred in a low and similar incidence across different treatment groups.

2.6.3. Serious adverse event / deaths / other significant events

In Pool A, SAEs occurred in a similar incidence in all treatment groups: 21% placebo, 18% BG00012 BID, 15% BG00012 TID, and 17% GA, with MS relapse being the most frequently mentioned serious AE (14% placebo, 10% BG00012 BID, 8% BG00012 TID, and 10% GA).

Flushing related events

Serious flushing events occurred in a low number in BG00012 240mg BID- and TID-treated subjects (<1% each) and all patients recovered after treatment discontinuation. However, in three of the four SAEs, flushing was suggestive of hypersensitivity reactions rather than the severe end of the spectrum of the flushing known to be caused by BG00012. All three of these patients required hospital treatment including parenteral steroids. Hypotension was reported in one patient and another patient had shortness of breath. These findings were considered as a clear indicator that the clinical diagnosis was probable hypersensitivity reaction of clinically important severity.

GI related events

Serious GI events happened in <1% of placebo-treated subjects and in 1% of BG00012-treated subjects each. The incidence of serious GI events was slightly higher with BG00012 treatment than with placebo (Study 109MS301: <1% placebo, 1% BG00012 BID, 1% BG00012 TID; Study 109MS302: <1% placebo, <1% BG00012 BID, 1% BG00012 TID, 0% GA). Patients recovered following treatment discontinuation or with intervention on continued treatment. .

Skin related events

Serious skin events were low and similar in all treatment groups: one patient from the placebo group experienced allergic dermatitis in study 109MS301. One Stevens - Johnson syndrome occurred in study 109MS301 in a BG00012 BID treated subject with concomitant carbamazepine. Two further subjects on BG00012 TID suffered from a skin-related event, one in study 109MS301 (pruritus; flushing), and one in study 109MS303 with allergic dermatitis.

Infections

SAEs reports related to infections were 33 out of 1720 patients for BG00012 (1.92%), compared with 12 out of 836 patients in the placebo group (1.44%), representing a 33% increase for the BG00012 group compared to placebo. The numbers were rather low and the significance of such difference is not known. In the individual studies, the incidence and nature of serious infections was similar in placebo and BG00012-treated patients (Study 109MS301: 2% in each group; Study 109MS302: 1% placebo, 2% BG00012 BID, 2% BG00012 TID, 1% GA). In both studies the most common type of serious infection was gastroenteritis (Study 109MS301: 0% placebo, <1% BG00012 BID, <1% BG00012 TID; Study 109MS302: 0% placebo, <1% BG00012 BID, <1% BG00012 TID, 0% GA). The excess incidence of gastroenteritis as an SAE in BG00012-treated patients over placebo was apparent. Excluding gastroenteritis, the incidence of infections as SAEs was the same in the BG00012 and placebo groups. Infective illness SAEs did not seem to be related to leukopenia or lymphopenia.

Cardiac related events

Serious cardiac disorder events were low but occurred in the BG00012 TID group only (0% placebo, 0% BG00012 BID, <1% BG00012 TID). One subject in the placebo group and one in the BG00012 TID group experienced significant ischemic cardiac events. In the uncontrolled study 109MS303, three additional potential ischemic cases were reported, one was rated a significant ischemic event (acute MI).

In Pool D, serious potential ischemic CV events occurred in 7 (2%) of subjects treated with BG00012. Five subjects had confirmed or suspected myocardial infarction and two subjects had coronary artery disease. Six of seven subjects experienced these events in the uncontrolled setting. Six subjects were male and one female. Risk factors or a history of cardiac ischemia were described for all subjects. Five of these subjects recovered after hospitalization and two died (acute myocardial infarction and sudden death). Causality could not be drawn since psoriasis patients are known to be at higher risk for myocardial infarction and CV mortality compared to the general population.

Hepatic related events

Serious hepatic adverse events were reported for two placebo-treated patients (hepatic enzyme increased), in one female subject (cholestatic hepatitis; history of hyperbilirubinemia), and in another female subject (cholelithiasis; Study 109MS301) both receiving BG00012 BID. In Pool B, two additional serious hepatic events were noted, one of these events being a suicide due to paracetamol overdose.

Renal related events

The incidence of serious renal and urinary AEs was low (<1%) in all groups and no serious AE of renal failure was reported.

Suicide and depression

Serious adverse events with respect to depression and suicidal tendencies were rare and balanced across groups.

Deaths

A total of seven deaths were reported in the BG00012 clinical program with five deaths belonging to the BG00012 groups. Five of these deaths happened in the controlled studies 109MS301 and 109MS302, and two further deaths were reported in the uncontrolled setting (study 109MS303). Two of the five deaths from BG00012-treated subjects occurred due to road traffic accidents, one death was a completed suicide and two deaths resulted from MS relapse. No death was considered to be related to the study drug. Nevertheless, the two MS relapse deaths may have occurred due to a lack of efficacy of BG00012.

2.6.4. Laboratory findings

Haematology parameters

The predominant findings were a decrease in white blood cells (WBC) and lymphocyte counts in BG00012-treated patients compared to placebo.

Mean WBC counts were reduced from baseline following Week 4 through Week 48, with a plateau through Week 96 for BG00012 BID in Pool A (baseline: 6.93 x 10^9/L, Week 48: 5.96 x 10^9/L; mean percentage: 11%). Similar numbers were observed for BG00012 TID. Placebo and GA values were well above those for BG00012 (approximately 6.9 x 10^9/L for each time point for placebo and GA). At all time points, mean WBC values remained above LLN. Potentially clinically significant WBC

counts <3.0 x 10^9/L were higher in the BG00012 groups compared to placebo and GA (1% placebo, 7% BG00012 BID, 5% BG00012 TID, 2% GA).

Lymphocytes similarly decreased from baseline following Week 4 through Week 48, with a plateau through Week 96 for BG00012 BID in Pool A (baseline: 1.97 x 10^9/L, Week 48: 1.34 x 10^9/L; mean percentage: 30%). Reduction for lymphocytes in the BG00012 TID group was similar but less pronounced (baseline: 1.99 x 10^9/L, Week 48: 1.44 x 10^9/L), resulting in a mean percentage decrease from baseline of 25% at Week 48. Again, lymphocyte counts in both BG00012 groups were lower than in the placebo or GA group (approximately 1.9 x 10^9/L for each time point for placebo and GA). At all time points, mean lymphocyte counts remained above LLN. For lymphocytes, more subjects in the BG00012 BID and TID groups (28% and 21%, respectively) than in the placebo group (3%) had a potentially clinically significant abnormal value <0.8 × 10^9/L; 6% and 3% of subjects in the BG00012 BID and TID groups, respectively and <1% in the placebo group had lymphocyte counts <0.5 × 10^9/L. With GA, the incidence in these 2 categories of abnormal values (<0.8 and <0.5 × 10^9/L) was similar to placebo.

In 133 MS subjects (studies 109MS301/109MS302) , who completed 2 years of BG00012 treatment, the mean percentage decrease of lymphocytes at the last value of BG00012-treatment was 31.3% and changed to 25.6% at 4 weeks post last dose. In 130 MS subjects, who completed 1 year of BG00012 treatment (C-1900), 89 subjects received lower doses of BG00012, the mean percentage decrease of lymphocytes in these subjects at the last value of BG00012-treatment was 28.2% and changed to 17.9% at 4 weeks post last dose. In Pool A (n=299) , the mean percentage decrease of lymphocytes in these subjects at the last value of BG00012-treatment was 22.6% and changed to 19.3% at 4 weeks post last dose.

In Pool A, there was also an increase in mean values for eosinophils between baseline (0.134 × 10^9/L) and Week 4 (0.322 × 10^9/L) in the BG00012 BID group (compared to stable placebo values of 0.14 × 10^9/L). The increase from baseline was transient, with mean values returning to baseline (placebo levels) by Week 12. A similar transient increase in mean eosinophil counts from baseline (0.133 × 10^9/L) at Week 4 (0.282 × 10^9/L) was seen in the BG00012 TID group. Mean eosinophil values for GA-treated subjects also increased between baseline and Week 8, but this was less pronounced.

Liver function tests

ALT and AST mean values increased from baseline with BG00012 compared to placebo. The highest increase in ALT occurred at Week 4. Baseline mean values for ALT were 20.9 U/L for placebo and 21.4 U/L for BG00012 BID. At Week 4, mean ALT increased to 21.4 U/L in the placebo and to 32.8 U/L in the BG00012 BID group. In the BG00012 TID group, mean ALT exceeded the normal range (37.2 U/L) at Week 4. Mean ALT values returned to baseline values for BG00012 BID and TID around Week 32 to 40. A similar trend was shown for AST: baseline mean values were 19.8 U/L for placebo and 20.1 U/L for BG00012 BID-treated subjects. At Week 4, mean values increased to 24.9 U/L for BG00012 BID-treated subjects, whereas no increase was seen for the placebo group.

ALT and AST maximum post-baseline values were classified to ≤1 x ULN, >1 x ULN, ≥3 x ULN, >5 x ULN, >10 x ULN, and >20 x ULN. Most subjects from Pool A had post-baseline values of ALT and AST of <3 x ULN. ALT and AST maximum post-baseline values of ≥3 x ULN were detected for 5% and 2% in the placebo group, for 6% and 2% in each BG00012 group (BID and TID), and for 7% and 4% of subjects from the GA group. ALT and AST maximum post-baseline values of >5 x ULN were low and similar across treatment groups (ALT: 2% each group; AST: <1-1% each group). Higher maximum post-baseline values were of rare incidence (<1%). There were no cases fulfilling Hy`s Law (ALT or AST ≥3 x ULN and total bilirubin >2 x ULN).

Most subjects had maximum post-baseline total bilirubin levels of ≤1 x ULN (90%-93% across treatment groups) and 7%-10% of subjects across treatment groups had values of >1 x ULN.

Kidney function tests / Electrolytes

No clinically notable changes in mean values for BUN or creatinine over time for BG00012 BID and TID groups were observed and no relevant differences from the placebo group were seen. Normal ranges were not exceeded by mean values at all time points across treatment groups. Shifts to higher values were similar and low for these analytes.

Analysis of minimum post-baseline values of eGFR showed that the incidence of subjects with values consistent with mild renal impairment was, in fact, lower in the BG00012 240mg BID group compared to placebo (46% placebo, 29% BG00012 BID, 24% BG00012 TID, 47% GA) and there was no increased incidence of moderate to severe renal impairment (i.e. eGFR < 60) in minimum post baseline eGFR in the total BG00012 group (3% placebo, 3% BG00012 BID, 2% BG00012 TID, 4% GA). The eGFR was also found to slightly increase over time (observation period of 2 years) for BG00012 compared to placebo, simultaneously, serum creatinine decreased.

With respect to electrolytes (potassium, sodium, chloride, bicarbonate), more subjects in the BG00012 BID (16%) and TID (15%) groups than in the placebo (9%) and GA (10%) groups had shifts to high bicarbonate in Pool A (percentages in Pool B were lower).

Urinalysis

Incidence of subjects with 2 positive urinalyses for protein was 47% for placebo, 51% for BG00012 BID, 53% for BG00012 TID, and 56% for GA. There was no relevant difference in the incidence of subjects with 2 consecutively positive findings of proteinuria on urinalysis, and in the incidence of urinalysis with 3+ or 4+ protein in the different treatment groups.

Elevated urine ketones were reported for BG00012-treated subjects compared to placebo and GA: 21% BG00012 BID, 30% BG00012 TID, 5% placebo, and 4% GA. Shifts to high/positive values in the BG00012 BID and TID groups were 63% and 68% compared to 26% placebo for urine ketones.

ß2-Microglobulin and microalbumin

In studies 109MS301, 109MS302 and 109MS303, more than 95% [85%] of subjects had ß2-microglobulin [microalbumin] values within the normal range (≤0.29 mg/L) [≤1.8 mg/dL] at baseline and all subsequent time points. Subjects, whose values of ß2-microglobulin or microalbumin exceeded the normal range, remained on these values throughout the study. A similar incidence of shifts to high urine β2-microglobulin was observed across the placebo, BG00012 BID and TID, and GA groups (9% to 10%, each group) based on pooled data from Studies 109MS301 and 109MS302. A higher percentage of subjects in both the BG00012 BID (36%) and TID (37%) groups had shifts to high in urine microalbumin when compared with placebo (29%) and GA (33%).

Vital signs

Body temperature, pulse, systolic and diastolic blood pressure, and change in body weight were monitored. There was no information on a clinically significant difference in any of the vital signs or change in body weight described of BG00012, placebo, or GA-treated subjects. ECGs were also performed at baseline and at 12-week intervals through Week 48 in study C-1900, and at baseline and every 24 weeks in studies 109MS301 and 109MS302. There were no relevant changes in QTc interval or any other quantitative or qualitative ECG parameters.

Other parameters

Serum lipid levels (HDL, LDL, triglycerides) were monitored in studies C-1900, 109MS301 and 109MS302. Favourable effects of BG00012 over placebo and GA were shown producing slightly higher mean HDL and lower mean triglyceride levels (the same was shown for shifts to high/low values).

Parathyroid hormone and Vitamin D levels were monitored in order to substantiate preclinical findings in rats with renal failure. Studies 109MS301 and 109MS302 showed increased mean parathyroid hormone levels from Week 48 to Week 96 and decreased Vitamin D levels (-20% of baseline values) in BG00012-treated subjects compared to placebo.

In a subgroup analysis, there were slightly more BG00012-treated subjects with low serum 1,25-dihydroxyvitamin D levels (<LLN) or elevated serum PTH (>ULN) compared to placebo with proteinuria (8% placebo vs. 12% BG00012 240 mg BID and 12% BG00012 240 mg TID). Patient without low serum 1,25-dihydroxyvitamin D levels or without elevated serum PTH, had proteinuria in a similar percentage: 8% placebo vs. 8% BG00012 240 mg BID and 11% BG00012 240 mg TID. However, decreased 1,25-dihydroxyvitamin levels were not observed in patients with ESRD.

2.6.5. Safety in special populations

No trials have been performed in any special multiple sclerosis patient populations. Patient with significant cardiovascular, pulmonary, gastrointestinal, dermatologic, psychiatric, neurologic (other than MS), renal impairment, hepatic conditions as well as HIV and Hepatitis C and B patients were excluded from the pivotal trials.

Recommendations for patients with renal, hepatic impairment and other special populations (paediatric, elderly) are discussed under clinical pharmacology (see 2.4.4).

In MS studies, females of child bearing potential were required to practice effective contraception. Nonetheless, there have been 56 pregnancies in the BG00012 clinical development program, of which 38 pregnancies were reported in subjects exposed to BG00012 (37 subjects with MS and 1 healthy volunteer) as of 02 January 2013. Pregnancy outcomes were known for 34 of the BG00012-exposed subjects and included 22 live births, 3 spontaneous abortions, and 9 elective terminations; information was pending on 3 pregnancies and 1 subject was lost to follow-up. No foetal abnormalities (i.e. congenital defects) have been reported for any of the pregnancies in the BG00012 clinical program.

2.6.6. Safety related to drug-drug interactions and other interactions

No specific investigation has been conducted in MS patient populations.

In Pool A, there was a higher number of patients with concomitant nephrotoxic medication suffering from renal and urinary adverse events compared to those patients who did not receive potentially nephrotoxic drugs: incidence of AEs with PNM: 21% placebo, 25% BG00012 BID, 26% BG00012 TID, 25% GA: without PNM: 16% placebo, 15% BG00012 BID, 18% BG00012 TID, 11% GA.

In Pool A, a significant percentage of AEs were also reported by all subjects treated with IV corticosteroids (100%) and by most subjects not treated with IV corticosteroids (placebo, 87%; BG00012 BID, 94%; BG00012 TID, 91%). A slight increase in the rate of infections could be observed in subjects treated with IV corticosteroids compared to subjects treated without i.v. corticosteroids (59% [54%] placebo, 63% [59%] BG00012 BID, 66% [58%] BG00012 TID, and 55% [47%] GA), for all treatment groups. A protective effect of corticosteroids was found for AEs related to flushing, which were reported by 27% of BG00012 BID-treated subjects versus 8% of placebo-treated subjects, while among subjects without IV corticosteroids flushing was reported by 37% of BG00012 BID-treated subjects versus 3% of placebo-treated subjects.

2.6.7. Discontinuation due to adverse events

In Pool A, discontinuations from study treatment due to AEs were slightly higher in BG00012-treated subjects compared to placebo and GA (11% placebo, 14% BG00012 240mg BID and TID each, and 10% GA). The most common AE leading to discontinuation from treatment was MS relapse (placebo 6% vs. 1% BG00012 240mg BID, 2% BG00012 240mg TID and 2% GA).

Adverse events leading to study drug discontinuation with higher incidences in BG00012-treated subjects compared to placebo and GA were reported for GI disorders (<1% placebo, 4% BG00012 BID, 6% BG00012 TID, <1% GA), flushing (<1% placebo, 3% BG00012 BID, 2% BG00012 TID, 0% GA), and for skin and subcutaneous disorders (<1% placebo, 2% BG00012 BID, 2% BG00012 TID, <1% GA). Other adverse events leading to study drug discontinuation were most of all single cases. Similar findings were noted for Pool B.

AEs that led to withdrawal from the study happened in a higher percentage in BG00012 treated subjects compared to placebo and GA (4% placebo, 8% BG00012 BID and TID each, and 3% GA). The pattern of AEs leading to withdrawal from the study was similar to that observed for AEs leading to discontinuation of study treatment.

Regarding the overall discontinuation reasons, the only differences in treatment discontinuations between placebo and BG00012 groups were MS relapse (higher for placebo-treated subjects) and adverse events (higher for BG00012-treated subjects). Data from studies 109MS301 and 109MS302 indicated a higher discontinuation rate for patients on BG00012 compared to placebo for the first year (the first three months) of treatment. This may be associated with occurrence of flushing and GI events which were highest during the first months of treatment.

In Pool A, the overall incidence of AEs leading to dose reductions was higher in the BG00012 groups (10% each) compared to the placebo group (2%). Higher incidences for dose interruptions due to laboratory abnormalities or AEs were also found for the BG00012 groups as compared to placebo (13-15% compared to 9%).

2.6.8. Post marketing experience

BG00012 has not been approved or marketed in any countries. Safety experience was made available on a medicinal product which contains dimethyl fumarate as one of its active substance component and marketed in Germany (Fumaderm).

In general, the adverse event profile for BG00012 and Fumaderm was similar, however hepatic adverse events were not seen as strongly indicative of a causal association with treatment.

There were three subjects on Fumaderm, who experienced PML (progressive multifocal leukencephalopathy). Two of the three subjects had risk factors (efalizumab treatment and malignancy, sarcoidosis treated with methotrexate and steroids). There was 1 case of PML without clear risk factors in 174,000 person-years of Fumaderm exposure (as of September 2012). During this evaluation, an additional case of PML was reported by the applicant in December 2012. This case was reported for a compounded formulation containing dimethyl fumarate (DMF) and another fumarate (copper monoethylfumarate), the patient was on treatment for 6 to 7 years. Severe lymphopenia was detected in all of these patients.

2.6.9. Discussion on clinical safety

The safety profile of DMF has been characterised with data from 2560 RRMS patients, accounting for around 3600 person-years of exposure. A total of 1469 subjects have been exposed for ≥1 year and 1095 for (≥2 years) at or above the recommended dose.

In MS clinical studies, the overall incidence of adverse events was slightly higher for BG00012 compared to controls (placebo or glatiramer acetate, GA) and ranged between 87-95% of subjects in all treatment groups.

The system organ class (SOC) with the highest proportion of patients with AEs was infections and infestations with an incidence of AEs slightly higher for subjects from the BG00012 BID and TID group (60% each) compared to subjects from the placebo and GA group (56% and 50%). Infections with the highest occurrence were nasopharyngitis, urinary tract infection, upper respiratory tract infection, influenza, sinusitis, bronchitis, and gastroenteritis. Serious infections were low in occurrence with gastroenteritis being the most common infection.

The safety profile indicated flushing, GI events and decreases in WBC and lymphocytes counts as important identified risks.

Serious cardiac disorder events were low but occurred in the BG00012 TID group only (0% placebo, 0% BG00012 BID, <1% BG00012 TID). One subject in the placebo group and one in the BG00012 TID group experienced significant ischemic cardiac events. In the uncontrolled study 109MS303, three additional potential ischemic cases were reported, one was rated a significant ischemic event (acute MI). In Pool D, serious potential ischemic CV events occurred in 7 (2%) of subjects treated with BG00012. Five subjects had confirmed or suspected myocardial infarction and two subjects had coronary artery disease. Six of seven subjects experienced these events in the uncontrolled setting. Risk factors or a history of cardiac ischemia were described for all subjects. Five of these subjects recovered after hospitalization and two died (acute myocardial infarction and sudden death). Causality could not be drawn since psoriasis patients are known to be at higher risk for myocardial infarction and CV mortality compared to the general population. Of note, patients with significant cardiovascular conditions were excluded from the clinical studies. According to CHMP request, a pooled analysis using the pivotal studies was provided to further investigate the risk of cardiovascular events under BG00012 treatment in relation to existing cardiovascular risk factors at baseline. Results showed no evidence for a higher risk in patients treated with BG00012, regardless of the dose administered. The overall numbers of events were similar in all treatment and dosing groups except for a slightly higher AE rate for tachycardia and palpitations in patients with risk factors at baseline. Single doses of DMF did not affect the QTc interval.

Flushing and related symptoms (hot flush, erythema, generalized erythema, burning sensation, skin burning, feeling hot and hyperaemia) were reported with an overall 5-times higher incidence in BG00012 BID/TID-treated subjects compared to placebo and GA. These events were associated with a prostanglandin mediated mechanism. The incidence of flushing (including hot flush) and related symptoms was highest during the first 3 months of the studies, with a peak in Month 1 (6% placebo vs. 36% BG00012 BID, 35% BG00012 TID). The overall prevalence for flushing was 31% during the first month, dropping to about 24% in the second month, and only slightly if at all less in subsequent months. In three of the serious flushing events patients required hospital treatment including parenteral steroids, hypotension was reported in one patient and another patient had shortness of breath. These findings seemed a clear indicator that the clinical diagnosis was probable hypersensitivity reaction of clinically important severity. This information has been considered a relevant warning for the prescribers and was included in the SmPC.

GI disorders (diarrhoea, nausea, upper abdominal pain, abdominal pain, vomiting, dyspepsia, gastroenteritis, GI disorder) were reported at a higher incidence in BG00012-treated subjects compared to placebo and GA and occurred with a higher incidence during the first three months of BG00012 treatment. These AEs seem to settle down more than flushing, with overall prevalence in BG00012 BID and TID-treated subjects of 22 and 25% in the first month, 17 and 16% during the second month, and 6-12% and 8-12% in subsequent months.The mechanism of GI events is unknown and is intended to be further investigated as part of the Risk Management Plan.

WBC counts and lymphocytes decreased (not so in the placebo and GA group) from Week 4 to Week 48 in BG00012-treated subjects and with a plateau through Week 96. Mean decrease for the first year was 11% and 30% for WBC counts and lymphocyte counts. No corresponding serious infection was reported for clinically significant low lymphocyte counts. However, potentially clinically significant WBC counts $<3.0 \times 10^9$/L were higher in the BG00012 groups compared to placebo and GA (1% placebo, 7% BG00012 BID, 5% BG00012 TID, 2% GA). For lymphocytes, more subjects in the BG00012 BID and TID groups (28% and 21%, respectively) than in the placebo group (3%) had a potentially clinically significant abnormal value $<0.8 \times 10^9$/L; 6% and 3% of subjects in the BG00012 BID and TID groups, respectively and <1% in the placebo group had lymphocyte counts $<0.5 \times 10^9$/L. With GA, the incidence in these 2 categories of abnormal values (<0.8 and $<0.5 \times 10^9$/L) was similar to placebo. Analyses were performed and showed evidence for slight recovery of lymphocytes 4 weeks post dose (after study treatment discontinuation or completion). Nevertheless, these data were considered inconclusive, since the observation period was short. The CHMP therefore requested a specific study to investigate the effects of BG00012 on the immune response. This will include further data in relation to vaccination, lymphocyte subsets and immunoglobulin levels in RRMS patients. In addition, the SmPC recommends a complete blood count (i.e. within 6 months) prior to initiating treatment, after 6 months of treatment and every 6 to 12 months thereafter and as clinically indicated.

Renal and urinary adverse events were slightly increased with BG00012 treatment: 18% placebo, 19% BG00012 BID, 22% BG00012 TID, 17% GA). The most common AE in this SOC was proteinuria: 7% placebo, 9% BG00012 BID, 10% BG00012 TID, 9% GA. In addition, an increased incidence for renal and urinary AEs in patients receiving nephrotoxic medications (PNM) was noted. Hepatic adverse events were also slightly increased with BG00012 treatment and mainly comprised increased hepatic transaminases (ALT and AST) within the first 6 months of treatment. Renal and hepatic toxicity could not be deduced from the clinical data (small increases in AEs), however, animal data showed renal and liver toxicities associated with BG00012 treatment and the underlying mechanisms have not been confirmed. The CHMP therefore considered renal tubular injury and hepatic injury as important potential risks of BG00012, whereas proteinuria was considered as identified risk (derived from the postmarketing experience with Fumaderm). On the basis of the overall data on these events, the CHMP recommended monitoring of these events prior to treatment initiation, after 3 and 6 months of treatment, every 6 to 12 months thereafter and as clinically indicated.

Malignancies reported in the BG00012 groups were low and similar to placebo and GA (breast cancer, basal cell skin carcinoma, and breast neoplasm in the placebo group; transitional cell carcinoma of renal pelvis and basal cell skin carcinoma in the BG00012 BID group; breast cancer and cervix cancer in the BG00012 TID group; and cervix cancer, endometrial cancer, thyroid cancer, and basal cell skin carcinoma in the GA group). Eight additional malignancies were reported in the ongoing study 109MS303. Further long term data, included in the Risk Management Plan, are expected to investigate this potential risk.

In MS studies, females of child bearing potential were required to practice effective contraception. Nonetheless, there have been 56 pregnancies in the BG00012 clinical development program, of which 38 pregnancies were reported in subjects exposed to BG00012 (37 subjects with MS and 1 healthy volunteer) as of 02 January 2013. Pregnancy outcomes were known for 34 of the BG00012-exposed subjects and included 22 live births, 3 spontaneous abortions, and 9 elective terminations; information was pending on 3 pregnancies and 1 subject was lost to follow-up. No foetal abnormalities (i.e. congenital defects) have been reported for any of the pregnancies in the BG00012 clinical program. A Pregnancy Exposure Registry has been put in place to monitor the use in this special population.

Four PML cases were reported on products containing DMF. Two of the three subjects had risk factors. There was 1 case of PML without clear risk factor. An additional case of PML was reported for a compounded formulation containing DMF; the patient was on treatment for 6 to 7 years. Severe lymphopenia was detected in all of these patients. Because the DMF mechanism on MS is not completely understood, the CHMP recommended that PML should be considered as a potential risk.

In addition, according to the discussion on clinical pharmacology (see 2.4.4), a drug interaction study with oral contraceptives will be performed. Data from the ongoing study evaluating effects of aspirin or dose titration on flushing and gastrointestinal events following oral administration of BG00012 will be provided to further address these AEs.

2.6.10. Conclusions on the clinical safety

From the safety database all the adverse reactions reported in clinical trials have been included in the SmPC. Appropriate measures including additional pharmacovigilance activities and risk minimization activities (see 2.8) have been put in place to ensure safe and effective use of the product in the recommended indication.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 4 the PRAC considers by consensus that the risk management system for dimethyl fumarate (TECFIDERA) in the treatment of adult patients with relapsing multiple sclerosis (MS) is acceptable.

This advice is based on the following content of the Risk Management Plan:

- **Safety concerns**

Table 26. Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	Decreases in leukocyte and lymphocyte counts Flushing Gastrointestinal events Proteinuria
Important potential risks	Serious and opportunistic infections Malignancies Renal tubular injury Hepatic injury Ketonuria Effects on pregnancy outcome Extent of off-label use in indications other

	than RRMS (particularly psoriasis)
Important potential interactions	Nephrotoxic medications Oral contraceptive
Important missing information	Safety profile in patients over the age of 55 years Safety profile in children and adolescents Safety profile in patients with severe disability (EDSS over 6.5) Safety profile in patients with renal impairment Safety profile in patients with hepatic impairment Safety profile in patients with severe active gastrointestinal disease Interactions with anti-neoplastic or immunosuppressive therapies during concomitant administration Safety profile in patients with concomitant administration of other MS treatments

The PRAC agreed.

- **Pharmacovigilance plans**

Table 27. Ongoing and planned studies in the pharmacovigilance development plan

Activity/Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
Study 109MS303: A Dose-Blind, multicenter, extension study to determine the long-term safety and efficacy of two doses of BG00012 monotherapy in subjects with relapsing-remitting MS. **Category 3**	To evaluate the long-term safety profile of BG00012.	Decreases in leukocyte and lymphocyte counts Flushing Gastrointestinal events Proteinuria Serious and opportunistic infections Malignancies Renal tubular injury Hepatic injury	Ongoing	Final report Q4 2016
Study 109MS401: A multicenter, global, observational study to collect information on safety and to document the drug utilization of BG00012 when used in routine medical practice in the treatment of relapsing multiple sclerosis. **Category 3**	To determine the incidence, type, and pattern of serious adverse events (SAEs) in patients with MS treated with BG00012.	Decreases in leukocyte and lymphocyte counts Flushing Gastrointestinal events Proteinuria Serious and opportunistic infections Malignancies Renal tubular injury Hepatic injury Nephrotoxic medications Safety profile in patients over the age of 55 years Safety profile in children and	Draft protocol version 1	Final report Q4 2024; First analysis when 1000 patients have completed 6 months of treatment, yearly with PSUR thereafter;

		adolescents Safety profile in patients with severe disability (EDSS over 6.5) Safety profile in patients with renal impairment Safety profile in patients with hepatic impairment Safety profile in patients with severe active gastro-intestinal disease Interactions with anti-neoplastic or immunosuppressive therapies during concomitant administration Safety profile in patients with concomitant administration of other MS treatments		
Study 109MS409: Claims database study of utilization patterns of BG00012 in Germany (Drug Utilization Study) **Category 3**	To determine the extent of off-label use with BG00012.	Extent of off-label use in indications other than RRMS (particularly psoriasis) Safety profile in children and adolescents	Draft protocol version 1	Final report Q4 2019 First analysis when sufficient BG00012 exposure has been recorded in medical registry or electronic medical record databases.
Study 109MS402: BG00012 Pregnancy Exposure Registry **Category 3**	To prospectively evaluate pregnancy outcomes in women with MS who were exposed to BG00012 since the first day of their last menstrual period (LMP) prior to conception or at any time during pregnancy.	Effects on pregnancy outcome	Draft protocol version 1	Final report Q4 2020
Paediatric investigational study **Category 3**	To determine the safety profile in paediatric patients between ages of 10 and 17 years old.	Safety profile in children and adolescents	Draft plan (CHMP Paediatric Committee approved)	Final report Q4 2016
Study 109MS307: A randomized, open-label study to assess the effects of BG00012 on the immune	To investigate the effects of BG00012 on the immune response.	Decreases in leukocyte and lymphocyte counts Serious and opportunistic	Draft synopsis	Final report Q1 2015

response to vaccination and on lymphocyte subsets and immunoglobulin levels in subjects with relapsing remitting multiple sclerosis. **Category 3**		infections		
Study 109HV321: A randomized, double-blind, phase 3b study to evaluate effects of aspirin or dose titration on flushing and gastrointestinal events following oral administration of BG00012 dosed at 240 mg BID. **Category 3**	To further characterise gastrointestinal events and events of flushing and to investigate the role of prostaglandins.	Gastrointestinal events Flushing	Ongoing	Final report Q3 2013
In-vivo interaction study **Category 3**	To investigate the potential interaction between BG00012 and concomitantly administered oral contraceptives.	Oral contraceptive	Planned	Draft protocol Q3 2013; Final report Q3 2014;

*Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

The PRAC, having considered the data submitted, was of the opinion that the proposed post-authorisation pharmacovigilance development plan is sufficient to identify and characterise the risks of the product.

The PRAC also considered that the studies in the post-authorisation development plan are sufficient to monitor the effectiveness of the risk minimisation measures.

- **Risk minimisation measures**

Table 28. Summary table of Risk Minimisation Measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Identified risks		
Decreases in leukocyte and lymphocyte counts	*SmPC section 4.4 Special warnings and precautions:* TECFIDERA may decrease lymphocyte counts (see section 4.8). TECFIDERA has not been studied in patients with pre-existing low lymphocyte counts and caution should be exercised when treating these patients. Prior to initiating treatment with TECFIDERA, a recent complete blood count (i.e. within 6 months) should be available. Assessments of complete blood counts are also recommended after 6 months of treatment and every 6 to 12 months thereafter and as clinically indicated. *SmPC section 4.8 Undesirable effects:* In the placebo-controlled studies, most patients (>98%) had normal lymphocyte values prior to	None.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	initiating treatment. Upon treatment with TECFIDERA, mean lymphocyte counts decreased over the first year with a subsequent plateau. On average, lymphocyte counts decreased by approximately 30% of baseline value. Mean and median lymphocyte counts remained within normal limits. Lymphocyte counts $<0.5x10^9$/l were observed in <1% of patients treated with placebo and 6% of patients treated with TECFIDERA. A lymphocyte count $<0.2x10^9$/l was observed in 1 patient treated with TECFIDERA and in no patients treated with placebo. The incidence of infections (58% versus 60%) and serious infections (2% versus 2%) was similar in patients treated with placebo or TECFIDERA. An increased incidence of infections and serious infections was not observed in patients with lymphocyte counts $<0.8x10^9$/l or $0.5x10^9$/l. A transient increase in mean eosinophil counts was seen during the first 2 months of therapy.	
Flushing	*SmPC Section 4.2 Posology and method of administration:* Temporary dose reduction to 120 mg twice a day may reduce the occurrence of flushing and gastrointestinal adverse reactions. Within 1 month, the recommended dose of 240 mg twice a day should be resumed. TECFIDERA should be taken with food (see section 5.2). For those patients who may experience flushing or gastrointestinal adverse reactions, taking TECFIDERA with food may improve tolerability (see section 4.4, 4.5 and 4.8). *SmPC section 4.4 Special warnings and precautions:* <u>Flushing</u> In clinical trials, 40% of TECFIDERA treated patients experienced flushing. In the majority of patients who experienced flushing, it was mild or moderate in severity and occurred on initiation of treatment. In clinical trials, 3 patients out of a total of 2560 patients treated with TECFIDERA experienced serious flushing symptoms that were probable hypersensitivity or anaphylactoid reactions. These events were not life-threatening but led to hospitalisation. Prescribers and patients should be alert to this possibility in the event of severe flushing reactions (see section 4.2, 4.5 and 4.8). *SmPC section 4.5: Interaction with other medicinal products and other forms of interaction* Administration of 325 mg (or equivalent) non enteric coated acetylsalicylic acid, 30 minutes prior to TECFIDERA, over 4 days of dosing, did	None.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	not alter the pharmacokinetic profile of TECFIDERA and reduced the occurrence and severity of flushing in a healthy volunteer study. However, long term use of aspirin is not recommended for the management of flushing. Potential risks associated with aspirin therapy should be considered prior to co-administration with TECFIDERA. (see section 4.2, 4.4 and 4.8). *SmPC section 4.8 Undesirable effects:* Summary of the safety profile The most common adverse reactions (incidence ⩾10%) for patients treated with TECFIDERA were flushing and gastrointestinal events (i.e. diarrhoea, nausea, abdominal pain, abdominal pain upper). Flushing and gastrointestinal events tend to begin early in the course of treatment (primarily during the first month) and in patients who experience flushing and gastrointestinal events, these events may continue to occur intermittently throughout treatment with TECFIDERA. The most commonly reported adverse reactions leading to discontinuation (incidence >1%) in patients treated with TECFIDERA were flushing (3%) and gastrointestinal events (4%). Flushing In the placebo-controlled studies, the incidence of flushing (35% versus 4%) and hot flush (7% versus 2%) was increased in patients treated with TECFIDERA compared to placebo, respectively. Flushing is usually described as flushing or hot flush, but can include other events (e.g. warmth, redness, itching, and burning sensation). Flushing events tend to begin early in the course of treatment (primarily during the first month) and in patients who experience flushing, these events may continue to occur intermittently throughout treatment with TECFIDERA. In patients with flushing, the majority had flushing events that were mild or moderate in severity. Overall, 3% of patients treated with TECFIDERA discontinued due to flushing. The incidence of serious flushing, which may be characterised by generalised erythema, rash and/or pruritus, was seen in less than 1% of patients treated with TECFIDERA (see section 4.2, 4.4 and 4.5).	
Gastrointestinal events	*SmPC Section 4.2 Posology and method of administration:* Temporary dose reduction to 120 mg twice a day may reduce the occurrence of flushing and gastrointestinal adverse reactions. Within 1 month, the recommended dose of 240 mg twice a day should be resumed. TECFIDERA should be taken with food (see section 5.2). For those patients who may	None.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	experience flushing or gastrointestinal adverse reactions, taking TECFIDERA with food may improve tolerability (see section 4.4, 4.5 and 4.8). *SmPC section 4.4 Special warnings and precautions:* TECFIDERA has not been studied in patients with severe renal or severe hepatic impairment and caution should therefore be used in these patients (see section 4.2). *SmPC section 4.8 Undesirable effects:* <u>Summary of the safety profile</u> The most common adverse reactions (incidence ⩾10%) for patients treated with TECFIDERA were flushing and gastrointestinal events (i.e. diarrhoea, nausea, abdominal pain, abdominal pain upper). Flushing and gastrointestinal events tend to begin early in the course of treatment (primarily during the first month) and in patients who experience flushing and gastrointestinal events, these events may continue to occur intermittently throughout treatment with TECFIDERA. The most commonly reported adverse reactions leading to discontinuation (incidence >1%) in patients treated with TECFIDERA were flushing (3%) and gastrointestinal events (4%). <u>Gastrointestinal</u> The incidence of gastrointestinal events (e.g. diarrhoea [14% versus 10%], nausea [12% versus 9%], upper abdominal pain [10% versus 6%], abdominal pain [9% versus 4%], vomiting [8% versus 5%] and dyspepsia [5% versus 3%]) was increased in patients treated with TECFIDERA compared to placebo, respectively. Gastrointestinal events tend to begin early in the course of treatment (primarily during the first month) and in patients who experience gastrointestinal events, these events may continue to occur intermittently throughout treatment with TECFIDERA. In the majority of patients who experienced gastrointestinal events, it was mild or moderate in severity. Four per cent (4%) of patients treated with TECFIDERA discontinued due to gastrointestinal events. The incidence of serious gastrointestinal events, including gastroenteritis and gastritis, was seen in 1% of patients treated with TECFIDERA (see section 4.2).	
Proteinuria	*SmPC Section 4.4 Special warnings and precautions for use:* TECFIDERA has not been studied in patients with severe renal or severe hepatic impairment and caution should therefore be used in these patients (see section 4.2).	None.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	SmPC section 4.8 Undesirable effects: Undesirable effect: Proteinuria Frequency category: Common	
Potential risks		
Serious and opportunistic infections	*SmPC section 4.4 Special warnings and precautions for use:* TECFIDERA may decrease lymphocyte counts (see section 4.8). TECFIDERA has not been studied in patients with pre-existing low lymphocyte counts and caution should be exercised when treating these patients. Prior to initiating treatment with TECFIDERA, a recent complete blood count (i.e. within 6 months) should be available. Assessments of complete blood counts are also recommended after 6 months of treatment and every 6 to 12 months thereafter and as clinically indicated. <u>Infections</u> In phase III placebo-controlled studies, the incidence of infections (60% vs 58%) and serious infections (2% vs 2%) was similar in patients treated with TECFIDERA or placebo, respectively. There was no increased incidence of serious infections observed in patients with lymphocyte counts $<0.8x10^9$/L or $<0.5x10^9$/L. During treatment with TECFIDERA in the MS placebo controlled trials, mean lymphocyte counts decreased by approximately 30% from baseline at one year and then plateaued (see section 4.8). Mean lymphocyte counts remained within normal limits. If a patient develops a serious infection, suspending treatment with TECFIDERA should be considered and the benefits and risks should be reassessed prior to re-initiation of therapy. Patients receiving TECFIDERA should be instructed to report symptoms of infections to a physician. Patients with serious infections should not start treatment with TECFIDERA until the infection(s) is resolved. *SmPC section 4.8 Undesirable effects:* In the placebo-controlled studies, most patients (>98%) had normal lymphocyte values prior to initiating treatment. Upon treatment with TECFIDERA, mean lymphocyte counts decreased over the first year with a subsequent plateau. On average, lymphocyte counts decreased by approximately 30% of baseline value. Mean and median lymphocyte counts remained within normal limits. Lymphocyte counts $<0.5\times10^9$/L were observed in <1% of patients treated with placebo and 6% of patients treated with TECFIDERA. A lymphocyte count $<0.2x10^9$/l was observed in 1 patient treated with TECFIDERA and in no patients treated with placebo. The incidence of infections (58% versus 60%) and serious infections (2% versus 2%) was similar	None.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	in patients treated with placebo or TECFIDERA. An increased incidence of infections and serious infections was not observed in patients with lymphocyte counts $<0.8\times10^9$/L or 0.5×10^9/L. A transient increase in mean eosinophil counts was seen during the first 2 months of therapy.	
Malignancies	*SmPC section 5.3 Preclinical safety data:* Carcinogenesis Carcinogenicity studies of dimethyl fumarate were conducted for up to 2 years in mice and rats. Dimethyl fumarate was administered orally at doses of 25, 75, 200 and 400 mg/kg/day in mice, and at doses of 25, 50, 100, and 150 mg/kg/day in rats. In mice, the incidence of renal tubular carcinoma was increased at 75 mg/kg/day, at equivalent exposure (AUC) to the recommended human dose. In rats, the incidence of renal tubular carcinoma was increased at 100 mg/kg/day, approximately 3 times higher exposure than the recommended human dose. The relevance of these findings to human risk is unknown. The incidence of squamous cell papilloma and carcinoma in the nonglandular stomach (forestomach) was increased at equivalent exposure to the recommended human dose in mice and below exposure to the recommended human dose in rats (based on AUC). The forestomach in rodents does not have a human counterpart.	None.
Renal tubular injury	*SmPC section 4.4 Special warnings and precautions for use:* Changes in renal and hepatic laboratory tests have been seen in clinical trials in subjects treated with TECFIDERA (see section 4.8). The clinical implications of these changes are unknown. Assessments of renal function (e.g. creatinine, blood urea nitrogen and urinalysis) are recommended prior to treatment initiation, after 3 and 6 months of treatment, and every 6 to 12 months thereafter and as clinically indicated. Assessments of hepatic function (e.g. ALT and AST) are also recommended prior to treatment initiation, after 3 and 6 months of treatment, and every 6 to 12 months thereafter. *SmPC section 4.8 Undesirable effects:* Undesirable effect: Proteinuria Frequency category: Common *SmPC section 5.3 Preclinical safety data:* Kidney changes were observed after repeated oral administration of dimethyl fumarate in mice, rats, dogs, and monkeys. Renal tubule epithelial regeneration, suggestive of injury, was observed in all species. Renal tubular hyperplasia was observed in rats with life time	None.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	dosing (2 year study). Cortical atrophy was observed in dogs and monkeys, and single cell necrosis and interstitial fibrosis were observed in monkeys that received daily oral doses of dimethyl fumarate for 12 months, at 6 times the recommended dose based on AUC. The relevance of these findings to humans is not known.	
Hepatic injury	*SmPC section 4.4 Special warnings and precautions:* Changes in renal and hepatic laboratory tests have been seen in clinical trials in subjects treated with TECFIDERA (see section 4.8). The clinical implications of these changes are unknown. Assessments of renal function (e.g. creatinine, blood urea nitrogen and urinalysis) are recommended prior to treatment initiation, after 3 and 6 months of treatment, and every 6 to 12 months thereafter and as clinically indicated. Assessments of hepatic function (e.g. ALT and AST) are also recommended prior to treatment initiation, after 3 and 6 months of treatment, and every 6 to 12 months thereafter. *SmPC section 4.8 Undesirable Effects:* In placebo-controlled studies, elevations of hepatic transaminases were observed. The majority of patients with elevations had hepatic transaminases that were <3 times the upper limit of normal (ULN). The increased incidence of elevations of hepatic transaminases in patients treated with TECFIDERA relative to placebo was primarily seen during the first 6 months of treatment. Elevations of alanine aminotransferase and aspartate aminotransferase ⩾3 times ULN, respectively, were seen in 5% and 2% of patients treated with placebo and 6% and 2% of patients treated with TECFIDERA. There were no elevations in transaminases ⩾3 times ULN with concomitant elevations in total bilirubin >2 times ULN. Discontinuations due to elevated hepatic transaminases were <1% and similar in patients treated with TECFIDERA or placebo.	None.
Ketonuria	*SmPC section 4.8 Undesirable effects:* Undesirable effect: Ketones measured in urine Frequency category: Very common <u>Laboratory abnormalities</u> In the placebo-controlled studies, measurement of urinary ketones (1+ or greater) was higher in patients treated with TECFIDERA (44%) compared to placebo (10%). No untoward clinical consequences were observed in clinical trials.	None.
Effects on pregnancy outcome	*SmPC section 4.5 Interactions:* In vitro CYP induction studies did not demonstrate an interaction between TECFIDERA	None.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	and oral contraceptives. In vivo interaction studies have not been performed with oral contraceptives. Even though an interaction is not expected, non hormonal contraceptive measures should be considered with TECFIDERA (see section 4.6). *SmPC section 4.6 Pregnancy:* There are no or limited amount of data from the use of dimethyl fumarate in pregnant women. Animal studies have shown reproductive toxicity (see section 5.3). TECFIDERA is not recommended during pregnancy and in women of childbearing potential not using approriate contraception (see section 4.5). TECFIDERA should be used during pregnancy only if clearly needed and if the potential benefit justifies the potential risk to the foetus. *SmPC section 5.3 Preclinical safety data:* <u>Reproduction toxicity</u> Oral administration of dimethyl fumarate to male rats at 75, 250, and 375 mg/kg/day prior to and during mating had no effects on male fertility up to the highest dose tested (at least 2 times the recommended dose on an AUC basis). Oral administration of dimethyl fumarate to female rats at 25, 100, and 250 mg/kg/day prior to and during mating, and continuing to Day 7 of gestation, induced reduction in the number of estrous stages per 14 days and increased the number of animals with prolonged diestrus at the highest dose tested (11 times the recommended dose on an AUC basis). However, these changes did not affect fertility or the number of viable fetuses produced. Dimethyl fumarate has been shown to cross the placental membrane into fetal blood in rats and rabbits, with ratios of fetal to maternal plasma concentrations of 0.48 to 0.64 and 0.1 respectively. No malformations were observed at any dose of dimethyl fumarate in rats or rabbits. Administration of dimethyl fumarate at oral doses of 25, 100, and 250 mg/kg/day to pregnant rats during the period of organogenesis resulted in maternal adverse effects at 4 times the recommended dose on an AUC basis, and low fetal weight and delayed ossification (metatarsals and hindlimb phalanges) at 11 times the recommended dose on an AUC basis. The lower fetal weight and delayed ossification were considered secondary to maternal toxicity (reduced body weight and food consumption). Oral administration of dimethyl fumarate at 25, 75, and 150 mg/kg/day to pregnant rabbits during organogenesis had no effect on embryo-fetal development and resulted in reduced maternal body weight at 7 times the	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	recommended dose and increased abortion at 16 times the recommended dose, on an AUC basis. Oral administration of dimethyl fumarate at 25, 100, and 250 mg/kg/day to rats during pregnancy and lactation resulted in lower body weights in the F1 offspring, and delays in sexual maturation in F1 males at 11 times the recommended dose on an AUC basis. There were no effects on fertility in the F1 offspring. The lower offspring body weight was considered secondary to maternal toxicity.	
Extent of off-label use in indications other than relapsing MS (particularly psoriasis)	*SmPC section 4.1 Therapeutic indications:* Tecfidera is indicated for the treatment of adult patients with relapsing multiple sclerosis. *SmPC section 4.2 Posology and method of administration:* Treatment should be initiated under supervision of a physician experienced in the treatment of the disease.	None.
Important potential interactions		
Nephrotoxic medications	*SmPC section 4.5 Interactions:* Concurrent therapy with nephrotoxic medicinal products (such as aminoglycosides, diuretics, NSAIDs or lithium) may increase the potential of renal adverse reactions (e.g. proteinuria) in patients taking TECFIDERA (see section 4.8).	None.
Oral contraceptive	*SmPC section 4.5 Interactions:* In vitro CYP induction studies did not demonstrate an interaction between TECFIDERA and oral contraceptives. In vivo interaction studies have not been performed with oral contraceptives. Even though an interaction is not expected, non-hormonal contraceptive measures should be considered with TECFIDERA (see section 4.6).	None.
Important missing information		
Safety profile in patients over the age of 55 years	*SmPC section 4.2 Posology and method of administration:* Clinical studies of TECFIDERA had limited exposure to patients aged 55 years and above, and did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients (see section 5.2). Based on the mode of action of the active substance there are no theoretical reasons for any requirement for dose adjustments in the elderly.	None.
Safety profile in children and adolescents	*SmPC section 4.2 Posology and method of administration:* The safety and efficacy of TECFIDERA in children and adolescents aged 10 to 18 years have not been established in multiple sclerosis. No data are available. There is no relevant use of TECFIDERA in children aged less than 10 years	None.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	in multiple sclerosis.	
Safety profile in patients with severe disability (EDSS over 6.5)	No requirement for any risk minimization as no safety concern in patients with severe disability has yet been described.	None.
Safety profile in patients with renal impairment	*SmPC section 4.2 Posology and method of administration:* TECFIDERA has not been studied in patients with renal or hepatic impairment. Based on clinical pharmacology studies, no dose adjustments are needed (see section 5.2). Caution should therefore be used when treating patients with severe renal or severe hepatic impairment (see section 4.4). *SmPC section 4.4 Special warnings and precautions for use:* <u>Blood/Laboratory tests</u> Changes in renal and hepatic laboratory tests have been seen in clinical trials in subjects treated with TECFIDERA (see section 4.8). The clinical implications of these changes are unknown. Assessments of renal function (e.g. creatinine, blood urea nitrogen and urinalysis) are recommended prior to treatment initiation, after 3 and 6 months of treatment, and every 6 to 12 months thereafter and as clinically indicated. Assessments of hepatic function (e.g. ALT and AST) are also recommended prior to treatment initiation, after 3 and 6 months of treatment, and every 6 to 12 months thereafter. <u>Severe renal and hepatic impairment</u> TECFIDERA has not been studied in patients with severe renal or severe hepatic impairment and caution should therefore be used in these patients (see section 4.2).	None.
Safety profile in patients with hepatic impairment	*SmPC section 4.2 Posology:* TECFIDERA has not been studied in patients with renal or hepatic impairment. Based on clinical pharmacology studies, no dose adjustments are needed (see section 5.2). Caution should therefore be used when treating patients with severe renal or severe hepatic impairment (see section 4.4). *SmPC section 4.4 Special warnings and precautions for use:* <u>Blood/Laboratory tests</u> Changes in renal and hepatic laboratory tests have been seen in clinical trials in subjects treated with TECFIDERA (see section 4.8). The clinical implications of these changes are unknown. Assessments of renal function (e.g. creatinine, blood urea nitrogen and urinalysis) are recommended prior to treatment initiation, after 3 and 6 months of treatment, and every 6 to 12 months thereafter and as clinically indicated. Assessments of hepatic function (e.g. ALT and AST) are also recommended prior to	None.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	treatment initiation, after 3 and 6 months of treatment, and every 6 to 12 months thereafter. Severe renal and hepatic impairment TECFIDERA has not been studied in patients with severe renal or severe hepatic impairment and caution should therefore be used in these patients (see section 4.2).	
Safety profile in patients with severe active gastrointestinal disease	*SmPC section 4.4 Special warnings and precautions for use:* TECFIDERA has not been studied in patients with severe active gastrointestinal disease and caution should therefore be used in these patients. *SmPC section 4.8 Undesirable effects:* Gastrointestinal The incidence of gastrointestinal events (e.g. diarrhoea [14% versus 10%], nausea [12% versus 9%], upper abdominal pain [10% versus 6%], abdominal pain [9% versus 4%], vomiting [8% versus 5%] and dyspepsia [5% versus 3%]) was increased in patients treated with TECFIDERA compared to placebo, respectively. Gastrointestinal events tend to begin early in the course of treatment (primarily during the first month) and in patients who experience gastrointestinal events, these events may continue to occur intermittently throughout treatment with TECFIDERA. In the majority of patients who experienced gastrointestinal events, it was mild or moderate in severity. Four per cent (4%) of patients treated with TECFIDERA discontinued due to gastrointestinal events. The incidence of serious gastrointestinal events, including gastroenteritis and gastritis, was seen in 1% of patients treated with TECFIDERA (see section 4.2).	None.
Interactions with anti-neoplastic or immunosuppressive therapies during concomitant administration	*SmPC section 4.5 Interactions:* TECFIDERA has not been studied in combination with anti-neoplastic or immunosuppressive therapies and caution should therefore be used during concomitant administration. In multiple sclerosis clinical studies, the concomitant treatment of relapses with a short course of intravenous corticosteroids was not associated with a clinically relevant increase of infection.	None.
Safety profile in patients with concomitant administration of other MS treatments	*SmPC section 4.5 Interactions:* Commonly used medicinal products in patients with multiple sclerosis, intramuscular interferon beta-a and glatiramer acetate, were clinically tested for potential interactions with TECFIDERA and did not alter the pharmacokinetic profile of dimethyl fumarate.	None.

The CHMP endorsed this advice with changes.

These changes concerned the following elements of the Risk Management Plan:

As part of additional pharmacovigilance activities, the RMP included study 109MS307 entitled:

“A Randomized, Open-Label Study to Assess the Effects of BG00012 on the Immune Response to Vaccination and on Lymphocyte Subsets and Immunoglobulin Levels in Subjects with Relapsing Remitting Multiple Sclerosis” (109MS307)”.

This study is currently linked to the safety concerns “Decreases in leukocyte and lymphocyte counts“ (identified risk) and “Serious and opportunistic infections” (potential risk).

The CHMP recommended including reference in the RMP of the additional SmPC amendment requested after the PRAC advice was given. This relates to information in section 4.5 of the SmPC regarding data on vaccination in patients treated with DMF. Such information is recommended to be included in the RMP as “Important Missing Information”. Cross references were also recommended between the above mentioned safety concerns. In addition, the applicant proposed to further investigate the gastrointestinal safety profile in patients consuming strong alcoholic drinks in the planned observational study (109MS401). See Table 29. The CHMP also requested to update the RMP (routine risk minimisation measures) in line with the final wording of the SmPC.

Table 29

Activity/Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
Study 109MS401: A multicenter, global, observational study to collect information on safety and to document the drug utilization of BG00012 when used in routine medical practice in the treatment of relapsing multiple sclerosis. **Category 3**	To determine the incidence, type, and pattern of serious adverse events (SAEs) in patients with MS treated with BG00012.	Decreases in leukocyte and lymphocyte counts Flushing Gastrointestinal events Proteinuria Serious and opportunistic infections Malignancies Renal tubular injury Hepatic injury Nephrotoxic medications Safety profile in patients over the age of 55 years Safety profile in children and adolescents Safety profile in patients with severe disability (EDSS over 6.5) Safety profile in patients with renal impairment Safety profile in patients with hepatic impairment Safety profile in patients with severe active gastro-intestinal disease Interactions with anti-neoplastic or	Draft protocol version 1	Q4 2024 Dependent on market uptake and study recruitment.

		immunosuppressive therapies during concomitant administration Safety profile in patients with concomitant administration of other MS treatments Gastrointestinal safety profile in patients consuming strong alcoholic drinks		
Study 109MS307: A randomized, open-label study to assess the effects of BG00012 on the immune response to vaccination and on lymphocyte subsets and immunoglobulin levels in subjects with relapsing remitting multiple sclerosis. **Category 3**	To investigate the effects of BG00012 on the immune response.	Decreases in leukocyte and lymphocyte counts Serious and opportunistic infections Vaccination during concomitant administration	Draft synopsis	TBC after protocol finalisation

Underlined= additional changes

Taking into consideration the above, a revised RMP (version 5) was submitted and considered acceptable by the CHMP.

2.9. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10. New Active Substance Status

By a letter dated 18 September 2013, the European Commission (EC) requested the CHMP to assess if dimethyl fumarate is different from Fumaderm composed of dimethyl fumarate, calcium salt of ethyl fumarate, magnesium salt of ethyl hydrogen fumarate and zinc salt of ethyl hydrogen fumarate with a view to include an assessment of the new active substance ('NAS') status of dimethylfumarate in Tecfidera, as per applicant request. A new active substance is defined in that context as a chemical substance not previously authorised as a medicinal product in the European Union (Annex I to the Notice to Applicants VOLUME 2A, Procedures for marketing authorisation, CHAPTER 1, MARKETING AUTHORISATIONS, June 2013).

On 23 September 2013, the applicant submitted evidence and discussion as to why the active substance of Tecfidera, dimethyl fumarate, should be regarded as 'new' in the light of the Annex I of the NtA - Chapter I.

2.10.1. Quality aspects

For the decision of whether dimethyl fumarate is different from Fumaderm composed of dimethyl fumarate (DMF), calcium salt of ethyl fumarate, magnesium salt of ethyl hydrogen fumarate and

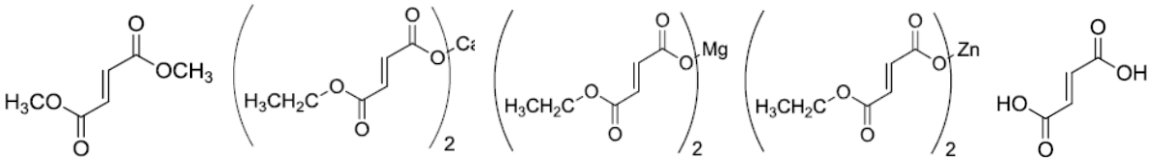
zinc salt of ethyl hydrogen fumarate (also called “monoethyl fumarate salts”), the following provision of Article 10(2)(b) has to be taken into account:

“The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy”.

Consequently, the chemical relationship of DMF and the monoethyl fumarate (MEF) salts should be taken into consideration.

DMF and MEF are different esters of fumaric acid (FA):

The chemical structures of the compounds under discussion are presented below:



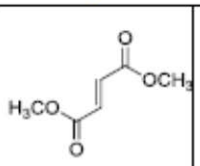
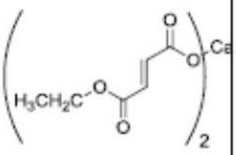
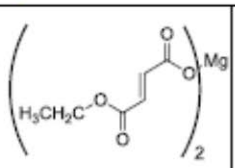
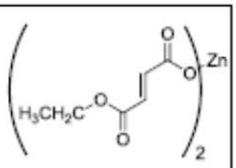
DMF MEF Ca^{2+} MEF Mg^{2+} MEF Zn^{2+} FA

It is clear that DMF and MEF contain the same backbone structure of fumaric acid (FA) and are different esters of fumaric acid. Although DMF and MEF are both esters of fumaric acid, this is of no relevance because Fumaric acid is not an active substance (as required under Article 10(2)(b) above) and is not itself authorised as a medicinal product in the European Union.

DMF and MEF have different physicochemical properties:

The applicant provided data on DMF and MEF with regard to key chemical differences, distinct physical properties, spectroscopic differences in solution, structural relationship and their chemical reactivity. The data support the conclusion that DMF and MEF are different esters with differential physicochemical properties including their molecular weights, melting points and water solubility, presented in the following table.

Table 1: Comparison of Physico-Chemical Properties of DMF and the MEF Salts

				
Cpd. Name	DMF	MEF•Ca	MEF•Mg	MEF•Zn
CAS registry number	624-49-7	62008-22-4	83918-60-9	62008-21-3
MW	144	326	311	351
Mpt (°C)	102	285	169	300
Water Solubility (mg/mL)	~1	294+/- 22	826 +/- 92	300 +/- 27
pKa[1]	No ionizable protons	3.3	3.3	3.3
LogD[1]	0.5	-2.75	-2.75	-2.75
Dipole Moment (debye)[2]	3.4	12.8	12.8	12.8

[1]Calculations based upon free acid; LogD (pH 6.5, jejunum and ileum) utilising the Percepta program (ACD labs);
[2]Calculation based on the anion for the salts: method: B3LYP/6-31G**5D; program package: Jaguar within the Schrödinger program package

As both DMF and MEF have shown to have pharmacological activity, it can be assumed that the two molecules may have different therapeutic moieties, i.e. dimethyl ester vs. mono-ethyl ester.

The assessment of the quality aspects is supported by the clinical and non-clinical assessment (see below).

Conclusions on quality aspects

In summary, DMF and MEF can be regarded as pharmaceutically different molecules, with distinct differences in regard to spectroscopic properties in solution, structural relationship, chemical reactivity, molecular weights, melting points and water solubility. DMF and MEF are different esters of fumaric acid, which itself is not an active substance.

Therefore, it is evident that DMF and the MEF salts are chemically distinct active substances.

2.10.2. Non Clinical aspects

Non clinical data on the pharmacodynamic and pharmacokinetic properties of DMF and the MEF salts components were presented as evidence to their pharmacological activities and different metabolic pathways, with the aim of supporting that the composition of Fumaderm (dimethyl fumarate and MEF salts) and Tecfidera (dimethyl fumarate) are different.

Pharmacodynamic activities of DMF and the MEF salts

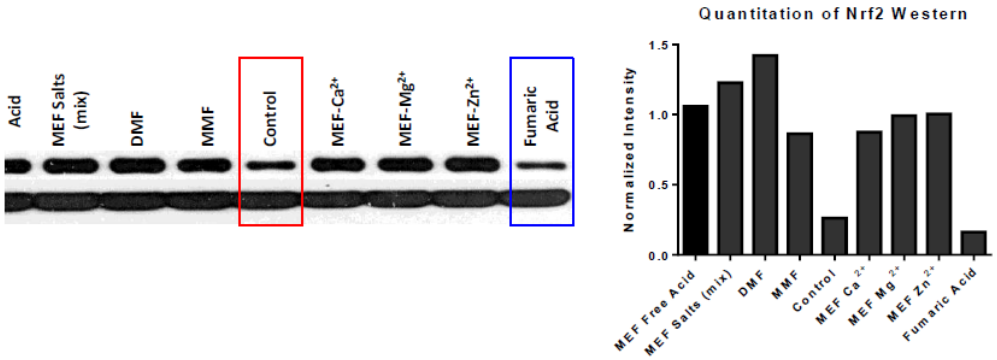
With the justification of the NAS claim for DMF, the applicant submitted new data to substantiate the pharmacological activity of the MEF salts contained in Fumaderm. In the *in vitro* studies, MEF salts were tested in a range of 0 – 12 µg/ml, which encompasses peak plasma concentrations that are known to occur in humans after oral dosing for MEF. Human concentrations are not known for fumaric acid. The literature indicates that after receiving a dose of Fumaderm, median human plasma exposures of MEF were 5.2 µM, which equates to approximately 1 µg/ml (Rostami-Yazdi *et al.,* 2010). However, plasma concentrations may not accurately reflect the exposure to MEF in certain tissues and locally in the intestinal mucosa, which would be expected to be much higher based on the site of absorption. Consequently, higher concentrations were also tested *in vitro*.

In all non-clinical studies, the ratio of the calcium, magnesium, and zinc salt mixtures of MEF was 87:5:3 MEF-Ca^{2+}, MEF-Mg^{2+}, MEF-Zn^{2+}, respectively, based on molecular weight. This reflects the ratio of the same MEF salts found in the Fumaderm product.

Overall, the newly provided investigations showed:

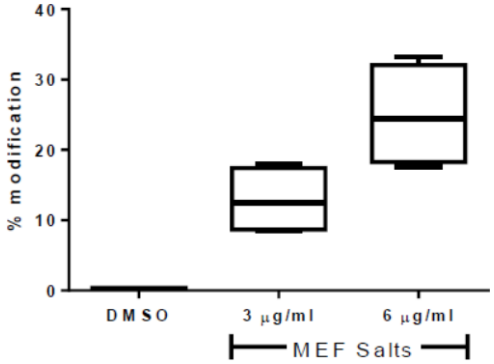
1) Induction of Nrf2 by either the individual Ca^{2+}, Mg^{2+} and Zn^{2+} salts of MEF or a mixture of the three MEF salts in COS-1 cells *in vitro*. DMF and MMF similarly increased Nrf2 concentrations as analysed by Western blotting, whereas fumaric acid was ineffective (Figure 21).

Figure 21: The Ca^{2+}, Mg^{2+} and Zn^{2+} salts of MEF increase Nrf2 in Cos-1 cells, whereas fumaric acid is ineffective



2) Covalent modification of Keap1 at Cys151 by a mixture of the Ca^{2+}, Mg^{2+} and Zn^{2+} salts of MEF as investigated by liquid chromatography and mass spectrometry in HEK293 cells *in vitro* (Figure 22). The same modification of Keap1 at Cys151 had been previously demonstrated for DMF and MMF *in vitro*.

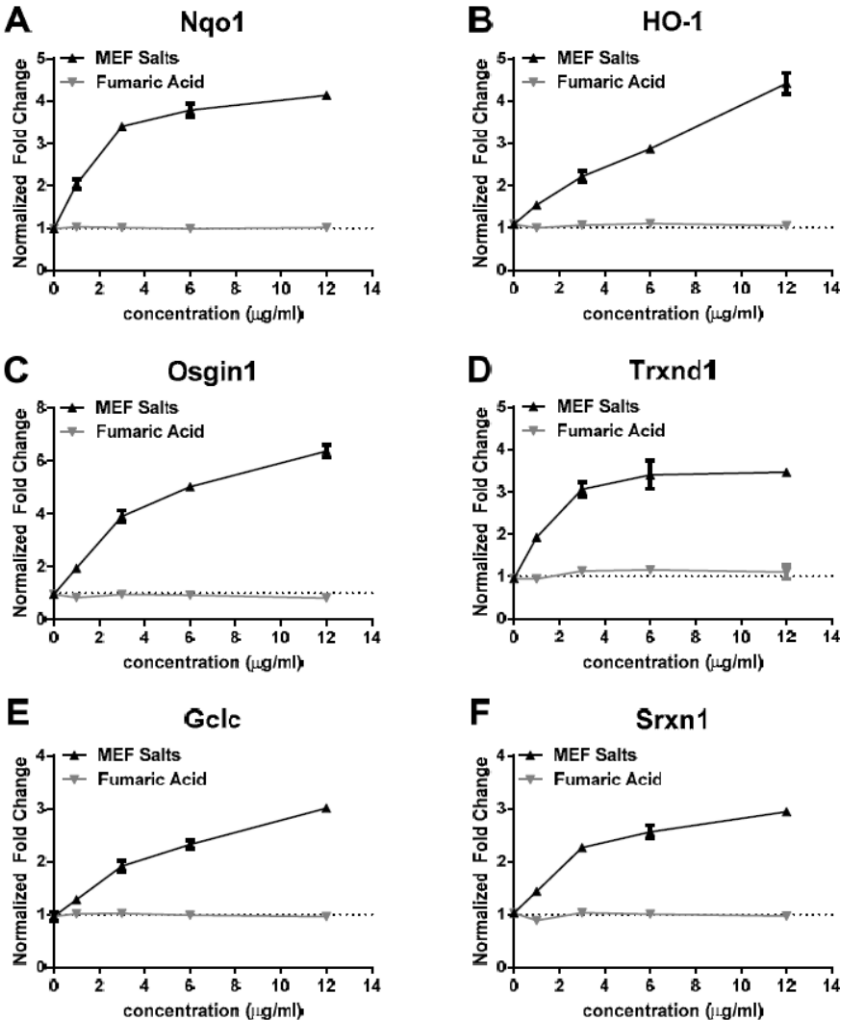
Figure 22 : The mixture of the Ca^{2+}, Mg^{2+} and Zn^{2+} salts of MEF modifies Keap1 at Cys151



3) Concentration-related induction of Nfr2-dependent gene expression by a mixture of the Ca^{2+}, Mg^{2+} and Zn^{2+} salts of MEF in human astrocytes *in vitro* as evident by RT-PCR analysis of the mRNA levels of NQO1, haeme oxygenase-1 (HO-1), sulfiredoxin 1 (Srxn 1), thioredoxin reductase 1 (Trxnd 1), oxidative stress-induced growth inhibitor 1 (Osgin 1) and glutamate-cysteine ligase catalytic subunit (Gclc). Fumaric acid was inactive to change expression of the evaluated genes *in vitro*. DMF and MMF were also stated to be active in this system, but no comparative data were provided.

The transcriptional profiles obtained for the mixture of MEF salts differed for the individual genes: at a concentration of >3 µg/ml, the Trxnd 1 response plateaued, while the slope (degree of relative increase) of NQO1 and Srxn1 responses decreased (Figure 23). In contrast, responses for HO-1, Osgin 1 and Gclc exhibited a linear increase across the entire concentration range. These differential gene responses suggest additional regulatory processes also govern expression or stability of these transcripts. Moreover, the pharmacological activity of the MEF salts appears to reside within the fumaric ester as fumaric acid itself did not produce a response.

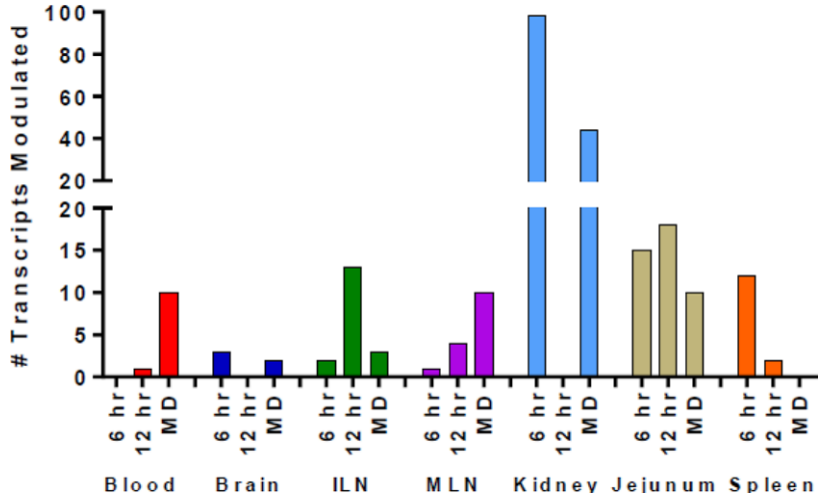
Figure 23: The mixture of the Ca^{2+}, Mg^{2+} and Zn^{2+} salts of MEF induces Nrf2-dependent gene expression



4) Induction of Nfr2-dependent gene expression by a mixture of the Ca^{2+}, Mg^{2+} and Zn^{2+} salts of MEF *in vivo*. C57Bl/6 mice received single or repeated oral doses of 79.2 mg/kg MEF salts for 10 days (equivalent to 100 mg/kg DMF). Fumaric acid was not tested due to its lack of activity in previous investigations *in vitro* (see above). Transcriptional responses were evaluated at 6 and 12 h after a single dose, and 12 h after the last dose following 10 consecutive days of once daily dosing (multiple dosing = MD). MEF pharmacokinetics were also assessed in plasma and tissues in separate cohorts of animals to verify drug exposure in these experimental paradigms.

Transcriptional profiling using Affymetrix gene chips revealed that the MEF salts significantly modified transcript levels in blood and all tissues examined (brain, inguinal lymph node (ILN), mesenteric lymph node (MLN), kidney, jejunum and spleen) with the most prominent response in the kidney (see Figure 24). DMF and MMF were also stated to be active in this system.

Figure 24: The mixture of MEF salts significantly modulates tissue-specific transcription *in vivo*



Pharmacokinetic properties of DMF and the MEF salts

In pharmacokinetic investigations in rats and dogs, DMF was rapidly absorbed from the gastrointestinal tract and converted pre-systemically to its active metabolite MMF. Quick absorption was also confirmed for MEF in these species. MMF was found to be further metabolised to fumaric acid, citric acid and glucose indicating initial DMF metabolism by esterases followed by the tricarboxylic acid cycle. Accordingly, DMF was found to be predominantly eliminated as CO_2.In contrast, the initial metabolic pathway of MEF appears different from DMF, but the metabolism of both substances converges at the level of fumaric acid, which is inactive and then further metabolised by the endogenous tricarboxylic acid cycle.

Newly submitted metabolism data obtained in hepatocyte suspensions in vitro also suggest formation of GSH conjugates of DMF. Other in vitro data indicate that MEF forms GSH conjugates as well and that DMF appears to be more reactive towards GSH than MEF. In hepatocytes, however, no MEF was found among DMF metabolites and only MMF together with a low amount of other minor metabolites were identified. Analyses using liver microsomes or hepatocytes from rats and humans further confirmed that MEF does not convert to either DMF or MMF and DMF or MMF are not transformed into MEF. In agreement with this finding, no MEF was detected in plasma or tissues of mice after oral administration of DMF, and, conversely, no DMF or MMF was identified in mice after oral administration of MEF. Overall, the presented data thus support that DMF and MEF have different pharmacokinetic properties and are not metabolites of each other in vivo.

Conclusions on non-clinical aspects

In non-clinical investigations, DMF and MEF independently demonstrated pharmacological activity by the regulation of Nrf2-dependent gene expression. The pharmacokinetic data further suggest that the initial metabolic pathway is different for both substances. In the first step, DMF is metabolised to MMF, however, MMF and MEF are metabolised differently. The metabolic pathways appear to converge at the level of fumaric acid, which is inactive and enters the endogenous tricarboxylic acid cycle. In addition, non-clinical data have shown that there is no metabolic interconversion between MMF and MEF or conversion of MEF to DMF or MMF in liver microsomes or hepatocytes from rats and humans. Both substances, DMF and MEF show different levels of glutathione (GSH) conjugation reactions.

2.10.3. Clinical Aspects

Clinical data on the pharmacodynamic and pharmacokinetic properties of DMF and the MEF salts components were presented as evidence to their pharmacological activities and different metabolic pathways, with the aim of supporting that the composition of Fumaderm (dimethyl fumarate and MEF salts) and Tecfidera (dimethyl fumarate) are different.

Pharmacodynamic activities of DMF, MEF salts and fumaric acid

DMF and MMF

DMF and its metabolite MMF have been shown to be pharmacologically active.

MEF

The available clinical data on MEF alone were derived from published literature and are limited. These confirmed the pharmacological activity seen preclinically and the most relevant data are summarised below:

1) Nieboer *et al.*, 1989

The applicant presented this publication describing therapeutic regimens of psoriasis with different fumaric acid esters and their salts. In all trials, efficacy was evaluated by a psoriasis severity score at 4 week intervals, whereas safety was assessed based on haematological and clinical chemistry parameters and adverse events. However, no pharmacokinetic data were presented. Relevant investigations and main findings are provided below:

Investigations	Main findings
I) Oral administration of a maximum dose of 240 mg Na-MEF (after titration over a three weeks period) was compared with placebo in 38 psoriasis patients for 4 months (double-blind design)	There was no difference between the numbers of improved, unimproved, or deteriorated cases in both groups. The average final score was the same in both groups, and so were the average final scores of each factor. Only the itching score showed a greater drop in the MEFAE-Na group than in the placebo group (not further specified).
II) Comparative study of 720 mg Na-MEF (n = 10) with the previous 240 mg Na-MEF dose (n = 10) in a subsequent study for 3 months	No difference was seen between the 720 mg versus the 240 mg regimen with regard to the number of improved patients. Significant differences ($p < 0.05$) were noted between the final scores of scaling and itching of both groups. The average final scores of the total groups and the extent of the eruption, the redness and the thickness were not different.
III) Oral administration of 240 mg DMF was compared with placebo in 42 psoriasis patients for 4 months (double-blind design). The treatment followed a similar schedule as study I	240 mg DMF treatment alone significantly improved disease symptoms in sub-study III within 6 weeks, as indicated by a drop to 60 % in the psoriasis severity score compared to a 105 % rise in the placebo group. However, 6 of 22 (27%) DMF-treated patients stopped medication due to serious gastrointestinal disorders during the first 2 weeks of the sub-study (nausea, diarrhoea, general malaise and stomachache).
IV) Open continuation study (following sub-study III) testing 240 mg DMF therapy in 56 patients. 13 of these patients had originally not responded to Na-MEF therapy. 10 and 20 of these patients had previously received 240 mg DMF and placebo, respectively. All patients were treated with doses from 60 to 240 mg per day and were observed for 4-9 months	In sub-study IV, DMF-treatment resulted in moderate improvement in 22 % and in a considerable improvement in 33 %of the patients, respectively. Irrespective of the DMF treatment, two patients presented with a serious relapse. Eleven patients (20 %) had to discontinue therapy due to serious gastrointestinal disorders.
V) Open study with fumaric acid compound therapy (FACT) in 36 psoriasis patients whose previous treatments had not been satisfactory. Medication started with one enteric-coated FAE-forte (120 mg DMF, 87 mg MEF-Na, 5 mg MEF-Ca, 3 mg MEF-Zn).	Of the 36 patients 23 showed an improvement of more than 50 % and 16 more than 90 %. Decreased itching and scaling usually began at the end of the first month of treatment.

Both 720 mg Na-MEF and 240 mg DMF doses produced mild disturbances of liver and kidney function, which disappeared following drug discontinuation.

Ninety percent (90%) of patients treated with MEF salts alone experienced flushing and tingling of skin (higher than observed with DMF alone). In addition, DMF selectively decreased suppressor T lymphocytes in about 50 % of the patients.

The authors stated that from studies I to IV it appeared that the gastrointestinal symptoms were caused mainly by DMFAE. The enteric-coated FAE-forte tablets (containing the mono-ethylester FA) in study V caused less frequent and less serious stomach pain and nausea (14/36 (39%)) than the enteric-coated DMFAE in studies III (16/22 (73%)) and V (29/56 (52%)). However, results may be biased by differences in the formulation: DMF was formulated as enteric-coated granulated capsules, whereas the exact formulation of Na-MEF is not known (described as “capsules”). An early release of approximately 80% of DMF from the enteric-coated granulated capsules resulted in the stomach may explain a higher percentage of gastrointestinal side effects with DMF alone. The CHMP also noted that treatment effects were seen earlier with DMF/MEF combination than with DMF alone.

2) Nieboer *et al.*, 1990

In a later double-blind trial comparing the effects of DMF (n = 22) single treatment with the DMF/MEF salt combination (n = 23) for 4 months, 50 % of the psoriasis patients in both study groups similarly revealed a considerable improvement in the psoriasis severity score. The authors stated that this percentage was even higher when one did not consider the initial study population, but only those patients who could be evaluated after 4 months. In that calculation the improvement percentage (i.e. a psoriasis severity score more than halved) was 55% in the DMF group and 80% in the DMF/MEF salt combination group. The course of the total score and of the separate parameters during the 4 months of the study showed a tendency towards a more rapid result with the DMF/MEF salt combination group than with the DMF single treatment.

Fumaric acid

According to the applicant, the inactivity of fumaric acid is uncontroverted and is confirmed by the European Commission Report of Scientific Committee on Animal Nutrition on the Safety of Fumaric Acid, adopted January 22, 2003, which concludes, “The fumarate esters (…) are effective in the immumodulation of psoriatic patients but not in healthy volunteers. There is no evidence fumaric acid shows comparable immunomodulating activity…” (See Section 4.3, Conclusion, page 11). The CHMP has also affirmed that fumaric acid is not active in Tecfidera noting DMF has been considered as the only active substance in Tecfidera and MMF is considered as the primary active metabolite of DMF.

Data on inactivity of fumaric acid were also derived from one literature reference suggesting that plasma levels of fumaric acid remained below the limit of detection following oral intake of Fumaderm (Rostami-Yazdi *et al.*, 2010).

Pharmacokinetic properties of DMF and the MEF salts

MEF is well absorbed and comprises a significant active fumarate exposure following administration of Fumaderm.

The in vitro and in vivo experiments indicate that DMF is metabolised to MMF and that MMF and MEF are metabolised differently. In addition, there is no metabolic interconversion between MMF and MEF or conversion of MEF to DMF or MMF in liver microsomes or hepatocytes from rats and humans.

Also, DMF and MEF differ in their degree of reactivity with nucleophiles, as evidenced by their different levels of glutathione (GSH) conjugation reactions. In addition to these data, a literature reference was presented (Rostami-Yazdi *et al.*, 2010) to support the difference in the

pharmacokinetic properties of DMF and MEF. The plasma levels of DMF, MMF and MEF were investigated in psoriasis patients after two doses of Fumaderm containing 120 mg DMF (MW: 144 g /mol) and 95 mg MEF (MW: 144 g /mol). The ratio between the $AUC_{0-\infty}$ of MMF and MEF is 2.1 to 1.0 [based on Median $AUC_{0-\infty}$ after dose correction].

Table 30: Pharmacokinetic parameters for MMF and MEF in plasma of three psoriasis patients after oral intake of two tablets of Fumaderm in a fasting state

Patient	t_{lag} (min)		t_{max} (min)		$t_{1/2}$ (min)		c_{max} (µM)		Cl (ml min^{-1} kg^{-1})		V (ml kg^{-1})		$AUC_{0-\infty}$ (min µg ml^{-1})	
	MMF	MEF	MMF	MEF	MMF	MEF	MMF	MEF	MMF	MEF	MMF	MEF	MMF	MEF
1	120	120	300	240	31.2	23.2	11.2	3.5	14.3	16.9	642.7	566.5	178.6	63.6
2	120	120	210	210	70.9	34.8	9.5	5.2	13.4	16.1	1373.7	810.1	129.8	51.1
3	120	120	210	210	38.7	25.4	13.7	6.4	15.4	16.1	860.9	589.6	172.0	68.1
Median	120	120	210	210	38.7	25.4	11.2	5.2	14.3	16.1	860.9	589.6	172	63.6

Together, these data indicate that DMF and MEF are distinct molecular entities and have unique activities.

Conclusions on clinical aspects

The evidence provided, although limited and based on literature precluding full assessment, support the non-clinical data and suggests that both DMF and MEF have pharmacological activities, with MEF showing activity alone in psoriasis both from an efficacy and safety/tolerability point of view. Pharmacokinetic data indicate that DMF and MEF are distinct molecular entities.

2.10.4. Overall discussion and Conclusions

The European Commission (EC) requested the CHMP to assess if dimethyl fumarate is different from Fumaderm composed of dimethyl fumarate (DMF), calcium salt of ethyl fumarate, magnesium salt of ethyl hydrogen fumarate and zinc salt of ethyl hydrogen fumarate (also called “monoethyl fumarate salts”) with a view to include an assessment of the new active substance (‘NAS’) status of DMF in Tecfidera, as per applicant request. The EC clarified that:

i) a new active substance under Directive 2001/83/EC is a chemical substance not previously authorised as a medicinal product in the European Union (Annex I to the Notice to applicants Volume 2A, Procedures for marketing authorisation, Chapter 1, Marketing authorisations, June 2013) and,

ii) dimethyl fumarate is part of the medicinal product Fumaderm authorised in 1994 in Germany, but it has not been previously authorised as a medicinal product in the European Union,

For the decision of whether dimethyl fumarate is different from Fumaderm composed of dimethyl fumarate, calcium salt of monoethyl fumarate, magnesium salt of monoethyl fumarate and zinc salt of monoethyl fumarate the following provision of Article 10(2)(b) (Directive 2001/83/EC) has been taken into account:

“The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy”.

Furthermore, Part II (3) of the Annex to the Directive states:

“Where the active substance of an essentially similar medicinal product contains the same therapeutic moiety as the original authorised product associated with a different salt/ester complex/derivative evidence that there is no change in the pharmaco-kinetics of the moiety,

pharmaco-dynamics and/or in toxicity which could change the safety/ efficacy profile shall be demonstrated. Should this not be the case, this association shall be considered as a new active substance."

In this context, the CHMP considered whether MEF and DMF are different active substances. The following points were considered in reaching this decision:

a) MEF and DMF are different esters of fumaric acid

From the CHMP's point of view, it is evident that DMF and the MEF salts contain the same backbone structure of fumaric acid (FA). They are also clearly different esters of fumaric acid (FA).

b) Fumaric acid is not an active substance and therefore it follows that it is the esters themselves that give the activity in both MEF and DMF.

DMF and its metabolite MMF have been shown to be pharmacologically active. It has also been established that fumaric acid is not a therapeutic moiety of DMF and is pharmacologically inactive. In vitro and in vivo non-clinical data including Nrf2-dependent gene expression together with published clinical data suggesting the pharmacological activity of MEF in psoriasis lead to the conclusion that DMF and MEF are both active.

c) The esters are different pharmaceutically (physicochemical properties) and do not inter-convert or follow the same metabolic path in-vivo.

The applicant provided data on DMF and MEF with regard to key chemical differences, distinct physical properties (melting point, molecular weight, aqueous solubility), spectroscopic differences in solution, structural relationship, and their chemical reactivity. Although this data on its own does not constitute an argument as to why the compounds should be considered different active substances, the impact of these properties on the different behaviour of MEF salts and DMF in the body supports the conclusion that DMF and MEF are different pharmaceutically.

The pharmacokinetic data further suggest that the initial metabolic pathway is different for both substances. The metabolic pathways appear to converge at the level of fumaric acid, which is inactive and enters the endogenous tricarboxylic acid cycle. In addition, there is no metabolic interconversion between MMF and MEF or conversion of MEF to DMF or MMF in liver microsomes or hepatocytes from rats and humans. Both substances, DMF and MEF, show different levels of glutathione (GSH) conjugation reactions.

Taking into consideration the above, the CHMP concluded that MEF and DMF are both active and are not the same active substance since they do not share the same therapeutic moiety (cf part II (3) of the Annex to Directive 2001/83/EC as amended).Therefore, the CHMP considered that there was no need to further investigate potential significant differences with regards to safety and/or efficacy properties.

Based on the review of data on the quality, non-clinical and clinical properties of both DMF and MEF, the CHMP considered that, the active substance of Tecfidera, dimethyl fumarate, is not the same as Fumaderm as MEF and DMF are considered pharmacologically active agents which contain different therapeutic moieties.

Based on the review of the scientific evidence, and in line with clarification provided by the European Commission above, it follows that dimethyl fumarate is different from Fumaderm composed of dimethyl fumarate, calcium salt of ethyl fumarate, magnesium salt of ethyl hydrogen fumarate and zinc salt of ethyl hydrogen fumarate. Therefore, the active substance of Tecfidera, dimethyl fumarate, is a new active substance.

3. Benefit-Risk Balance

Benefits

Beneficial effects

DMF (dimethyl fumarate) is a novel orally administered therapy for the treatment of patients suffering from relapsing-remitting multiple sclerosis. Beta-interferons require long-term parenteral injections and are considered to have a modest efficacy as compared to second line second-line disease modifying therapies (DMTs). However, these second-line DMTs carry greater risks including major morbidity and mortality (e.g. PML). BG00012 is claimed to fulfil an unmet medical need for an oral agent that is at least as effective as the currently available first-line treatments but without the serious undesirable effects of the available second-line DMTs.

The exact mechanism of action of DMF is unknown but it is thought to be mediated principally via activation of the nuclear factor (erythroid-derived 2)-related factor 2 (Nrf2) antioxidant response pathway. Additional effects for the regulation of the immune system such as anti-inflammatory actions have been shown in pre-clinical studies, although this was not clearly observed in the clinical setting.

Two large phase 3 pivotal studies (109MS301, 109MS302) over two years were conducted. The relative risk of relapse at 2 years by BG00012 BID and TID was reduced over placebo by 49% (hazard ratio of 0.51) and 50% (hazard ratio of 0.50), respectively, in study 109MS301, and by 34% (hazard ratio of 0.66) and 45% (hazard ratio of 0.55) in study 109MS302. The reduction in annualized relapse rate over placebo with BG00012 BID and TID was 53% (ratio rate of 0.47) and 48% (ratio rate of 0.52), respectively, in study 109MS301 and was 44% (ratio rate of 0.560) and 50.5 % (ratio rate of 0.495) in study 109MS302.

Patients defined as having at least one relapse while on ≥12 months therapy with beta-interferon, and having at least 9 T2- hyperintense lesions in cranial MRI or at least 1 Gd-enhancing lesion or having an unchanged or increased relapse rate were representing around 20 % of the population treated with BG00012 BID. Around 6% of BG00012 BID population also had 2 or more relapses in the year prior to enrolment and at least one Gd enhancing lesions. In these populations considered relevant for the definition of “high disease activity”, a consistent effect on relapses was shown.

Disability progression was measured in terms of time to a 12-week confirmed increase in EDSS score. In study 109MS301, both DMF tested doses reached statistical significance when compared to placebo in reducing the risk of 12-week sustained disability progression (240 mg BID: p=0.0050, 240 mg TID: p=0.0128). The hazard ratios were 0.62 and 0.66 for 240 mg BID and 240 mg TID groups, respectively.

From study 109MS302, a post-hoc analysis was provided of the treatment effects in BG00012 as compared to GA. In the majority of the primary and secondary endpoints, including the ARR and time to 3-month sustained disability), an effect in favour of BG00012 was observed. However, both DMF tested doses failed to reach statistical significance when compared to placebo in reducing the risk of 12-week sustained disability progression (240 mg BID: p=0.2536; 240 mg TID: p=0.2041). The hazard ratios were 0.79 and 0.76 for 240 mg BID and 240 mg TID groups, respectively.

Based on historical comparisons, there was a relative reduction for ARR of 44-53% under BG00012 compared to a relative reduction in ARR of around 30% for interferons and GA, suggesting at least comparable efficacy on relapses for BG00012 when compared to approved first-line treatment. However, the current second-line treatments provided even better results on this endpoint.

Uncertainty in the knowledge about the beneficial effects

A limited number of patients with high disease activity was included in the clinical studies. Most of the patients in all treatment groups experienced no relapses (109MS301: placebo: 58%, BG00012 240 mg BID: 76%, BG00012 240 mg TID: 77%; 109MS302: placebo: 61%, BG00012 240 mg BID: 74%, BG00012 240 mg TID: 78%, GA: 70%). Most of the patients had no Gd enhancing lesions at baseline, suggesting that patients in general were rather mild affected.

Although the efficacy on relapse was consistently shown across the studied population (including those subgroups defined as "high disease activity"), a lesser effect of BG00012 on relapses in patients with higher EDSS score at baseline, in non-naïve patients and in patients aged 40 years and above was observed in both pivotal studies.

Effect on disability progression was not that robust across the two pivotal studies. Statistical significance was reached for the first pivotal study, but not in study 109MS302. In both individual studies, a sensitivity analysis was performed in terms of 24-weeks sustained disability progression. Although, none of the BG00012 treatment arms reached statistical significance when compared to placebo, a similar trend as for 12 weeks confirmed disability progression was however noted. In the subgroups defined as "high disease activity", the effect for sustained disability on the endpoint time to 3-month sustained disability progression was not clearly established.

Efficacy data in patients who discontinued study drug were considered limited to evaluate a possible rebound effect. Additional Long term data are awaited to further investigate this issue as well as to confirm maintenance of the effect.

Conclusions on added clinical benefit versus existing available therapy could not be confirmed due to the design of the pivotal studies. Study 109MS301 did not include an active comparator. Study 109MS302 included glatiramer acetate but was not designed for a direct comparison with DMF. Historical comparisons were considered only as supportive of the efficacy in the intended MS population.

Risks

Unfavourable effects

Flushing, GI events, decreases in WBC and lymphocytes counts and proteinuria have been considered as important identified risks.

Flushing and related symptoms (hot flush, erythema, generalized erythema, burning sensation, skin burning, feeling hot and hyperaemia) were reported with an overall 5-times higher incidence in BG00012 BID/TID-treated subjects compared to placebo and GA. The overall prevalence for flushing was 31% during the first month, dropping to about 24% in the second month, and only slightly if at all less in subsequent months. The incidence of flushing (including hot flush) and related symptoms was highest during the first 3 months of the studies, with a peak in Month 1 (6% placebo vs. 36% BG00012 BID, 35% BG00012 TID). In three of the serious flushing events patients required hospital treatment including parenteral steroids.

GI disorders (diarrhoea, nausea, upper abdominal pain, abdominal pain, vomiting, dyspepsia, gastroenteritis, GI disorder) were reported at a higher incidence in BG00012-treated subjects compared to placebo and GA and occurred with a higher incidence during the first three months of BG00012 treatment. The overall prevalence in BG00012 BID and TID-treated subjects was 22 and 25% in the first month, 17 and 16% during the second month, and 6-12% and 8-12% in subsequent months.

WBC counts and lymphocytes decreased from Week 4 to Week 48 in BG00012-treated subjects and with a plateau through Week 96. Mean decrease for the first year was 11% and 30% for WBC counts and lymphocyte counts. No corresponding serious infection was reported for clinically

significant low lymphocyte counts. However, potentially clinically significant WBC counts <3.0 x 10^9/L were higher in the BG00012 groups compared to placebo and GA (1% placebo, 7% BG00012 BID, 5% BG00012 TID, 2% GA). For lymphocytes, more subjects in the BG00012 BID and TID groups (28% and 21%, respectively) than in the placebo group (3%) had a potentially clinically significant abnormal value <0.8 × 10^9/L; 6% and 3% of subjects in the BG00012 BID and TID groups, respectively and <1% in the placebo group had lymphocyte counts <0.5 × 10^9/L.

Renal and urinary adverse events were slightly increased with BG00012 treatment: 18% placebo, 19% BG00012 BID, 22% BG00012 TID, 17% GA). The most common AE in this SOC was proteinuria: placebo 7%, BG00012 BID 9%, BG00012 TID 10%, GA 9%. In addition, an increased incidence for renal and urinary AEs was noted in patients receiving nephrotoxic medications (PNM). The incidence of hepatic adverse events was similar in placebo and BG00012-treated patients (9% placebo vs. 9% BG00012 BID, 10% BG00012 TID, and 11% GA). However, elevations of liver transaminases were most often reported and of slightly higher incidence compared to placebo: ALT increased (5% placebo vs. 6% BG00012 BID and TID and GA each), AST increased (2% placebo vs. 4% BG00012 BID and TID and GA each). Increased hepatic enzymes were detected especially within the first 6 months of treatment. Most BG00012-treated subjects had post-baseline values of ALT and AST <3 x ULN. Although the safety profile did not reveal a detrimental effect of BG00012 on these AEs, animal data showed renal and liver toxicities associated with BG00012.

Uncertainty in the knowledge about the unfavourable effects

Flushing events may be prostaglandin mediated, however the mechanism has not been fully elucidated. The underlying mechanism for GI events is considered unknown. Given the importance of these events in the safety profile of DMF, additional data from the ongoing study evaluating effects of aspirin or dose titration on flushing and gastrointestinal events following oral administration of BG00012 are awaited and further investigations may need to be considered on the basis of these expected data.

Data are also lacking on the effect of BG00012 on immune response. A specific clinical study to investigate this effect in relation to vaccination, lymphocyte subsets and immunoglobulin levels in RRMS patients, has been included as part of the Risk Management Plan.

Malignancies reported in the BG00012 groups were low and similar to placebo and GA. Nevertheless, eight additional malignancies were reported in the ongoing study 109MS303. Further long term data, included in the Risk Management Plan, are expected to investigate this potential risk.

In MS studies, females of child bearing potential were required to practice effective contraception. Nonetheless, there have been 56 pregnancies in the BG00012 clinical development program, of which 38 pregnancies were reported in subjects exposed to BG00012 (37 subjects with MS and 1 healthy volunteer) as of 02 January 2013. A Pregnancy Exposure Registry has been put in place to monitor the use in this special population. In addition, the potential risk of interaction with oral contraceptives will be further investigated via a specific in vivo study.

Four PML cases were reported on products containing DMF. Severe lymphopenia was detected in all of these patients. Because the DMF mechanism on MS is not completely understood, PML is considered as a potential risk.

Benefit-risk balance

Importance of favourable and unfavourable effects

DMF (dimethyl fumarate) is a novel orally administered therapy for the treatment of patients suffering from relapsing-remitting multiple sclerosis. The exact mechanism of action of the DMF is unknown but it is thought to be mediated principally via activation of the nuclear factor (erythroid-derived 2)-related factor 2 (Nrf2) antioxidant response pathway; this new mechanism of action appeared to offer a relatively favourable safety profile, although further long term data are expected to monitor the potential and identified risks. The main risks for DMF included flushing, GI events, decreases in WBC and lymphocytes counts, proteinuria, and increases in liver transaminases and these were considered manageable with the proposed risk minimisation measures. Whilst the studied patient population generally presented a rather low disease activity across the studies, Tecfidera demonstrated a consistent effect on relapses compared to placebo to a statistically significant degree and this was also evident in a sufficiently represented group of patients with "high disease activity". The effect on disability progression was not that robust given the results between studies on the various endpoints for time to confirmed disability progression.

Benefit-risk balance

Having considered that the efficacy was sufficiently demonstrated across the RRMS population and that the identified risks were manageable with the proposed risk minimisation measures, the CHMP concluded that the benefit-risk balance for Tecfidera was positive for the following indication:

"Tecfidera is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (please refer to section 5.1 for important information on the populations for which efficacy has been established)".

4. Recommendations

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Tecfidera in the treatment of "adult patients with relapsing remitting multiple sclerosis" is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

In addition, an updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

New Active Substance Status

The CHMP considers that dimethyl fumarate is different from Fumaderm composed of dimethyl fumarate, calcium salt of ethyl fumarate, magnesium salt of ethyl hydrogen fumarate and zinc salt of ethyl hydrogen fumarate. Based on the review of the scientific evidence, and in line with clarification provided by the European Commission that:

i) a new active substance under Directive 2001/83/EC is a chemical substance not previously authorised as a medicinal product in the European Union (Annex I to the Notice to applicants Volume 2A, Procedures for marketing authorisation, Chapter 1, Marketing authorisations, June 2013) and,

ii) dimethyl fumarate is part of the medicinal product Fumaderm authorised in 1994 in Germany, but it has not been previously authorised as a medicinal product in the European Union,

the active substance of Tecfidera, dimethyl fumarate, is a new active substance.[2]

2 Post-opinion note: The NAS status at the time of the CHMP opinion was to be considered in the regulatory context provided by the Commission. Following further discussion of the regulatory context at the Standing Committee on Medicinal Products for Human Use, on 30 January 2014 the European Commission adopted, in accordance with the opinion of the Standing Committee, a decision granting a marketing authorisation for Tecfidera including the following recital: dimethyl fumarate (DMF), the active substance of "Tecfidera - Dimethyl fumarate", is part of the composition of the authorised medicinal product Fumaderm which consist of DMF and calcium salt of ethyl fumarate, magnesium salt of ethyl hydrogen fumarate and zinc salt of ethyl hydrogen fumarate (MEF salts), belonging to the same marketing authorisation holder. The Committee for Medicinal Products for Human Use concluded that MEF and DMF are both active and are not the same active substance since they do not share the same therapeutic moiety. Therefore it is considered that Tecfidera containing DMF is different from Fumaderm the other already authorised medicinal product composed of DMF and MEF salts. Therefore "Tecfidera - Dimethyl fumarate", the application of which was based on Article 8(3) of Directive 2001/83/EC, and the already authorised medicinal product Fumaderm do not belong to the same global marketing authorisation as described in Article 6(1) of Directive 2001/83/EC.

In view of this evolution of the regulatory considerations, as reflected in the recital of the Commission Decision, the final statement in the CHMP opinion that “the active substance of Tecfidera, dimethyl fumarate, is a new active substance” is obsolete. However, all the other scientific considerations and conclusions related to this assessment remain valid.