Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Dimethyl Fumarate

Proprietary Product Name: Tecfidera

Sponsor: Biogen Idec Australia Pty Ltd

October 2013

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
9HPT	Nine-Hole Peg Test
AE	adverse event
ANCOVA	analysis of covariance
AUC	area under the curve
BG00012	Tecfidera (dimethyl fumarate)
BID	twice daily
CI	confidence interval
C_{max}	maximum plasma concentration
CNS	central nervous system
CRF	case report form
CSR	clinical study report
DMF	dimethyl fumarate
DMT	disease modifying therapy
EDSS	Expanded Disability Status Scale
EQ-5D	European Quality of Life-5 Dimensions Health Survey
GA	glatiramer acetate

Abbreviation	Meaning
Gd	gadolinium
IFN β	interferon beta
IM	intramuscular
INEC	Independent Neurology Evaluation Committee
ITT	Intent-to-treat
IV	intravenous
IVMP	Intravenous methylprednisolone
MCS	Mental Component Summary
MMF	monomethyl fumarate
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSFC	Multiple Sclerosis Functional Composite
MTR	magnetization transfer ratio
Nrf2	nuclear factor (erythroid-derived 2) related factor 2
PASAT-3	3-Second Paced Auditory Serial Addition Test
PBVC	percent brain volume change
PCS	Physical Component Summary
PD	pharmacodynamics
PK	pharmacokinetics
PPMS	primary progressive multiple sclerosis
PRMS	progressive-relapsing multiple sclerosis
QD	once daily
RRMS	relapsing-remitting multiple sclerosis
SAE	serious adverse event
SF-36	Short Form-36® Health Survey
SC	subcutaneous
SIENA	Structural Image Evaluation of Normalized Atrophy

Abbreviation	Meaning
SPMS	secondary progressive multiple sclerosis
T25FW	Timed 25-Foot Walk
TID	3 times daily
VAS	Visual Analogue Scale

I. Introduction to product submission

Submission details

Type of submission	New Chemical Entity
Decision:	Approved
Date of decision:	3 July 2013
Active ingredient:	Dimethyl Fumarate
Product name:	Tecfidera[1]
Sponsor's name and address:	Biogen Idec Australia Pty Ltd PO Box 380, North Ryde BC NSW 1670
Dose form:	Modified release capsules
Strengths:	120 mg and 240 mg
Container:	Blister pack
Pack sizes:	14 and 112 capsules (120 mg) 14 and 56 capsules (240 mg)
Approved therapeutic use:	Tecfidera is indicated in patients with relapsing multiple sclerosis to reduce the frequency of relapses and to delay the progression of disability.
Route of administration:	Oral (PO)
Dosage:	The starting dose for Tecfidera is 120 mg twice a day orally. After 7 days, increase to the recommended dose of 240 mg twice a day orally
ARTG numbers:	197119 and 197118

Product background

This AusPAR describes and application by the sponsor Biogen Idec Australia Pty Ltd to register encapsulated enteric coated microtablets containing the new chemical entity dimethyl fumerate under the trade name Tecfidera.

The sponsor proposed the following indication in their application letter:

> *Tecfidera is indicated in patients with relapsing multiple sclerosis to reduce the frequency of relapses and to delay the progression of disability.*

The maximum recommended dose was proposed as 240 mg twice daily orally. A maximum duration of dosing was not specified.

[1] The tradename was amended during evaluation, from Neutrinza to Tecfidera. The tradename was amended in the USA as it was considered too similar to Neurontin. The new tradename was subsequently accepted by the TGA.

MS is characterised by the development of inflammatory plaques in the central nervous system including the brain, spinal cord and optic nerves. The primary process is inflammatory damage to the myelin of the central nervous system which may be reversible but axonal damage may also occur and leads to increasing permanent disability. MS also has a degenerative component and is associated with progressive brain atrophy.

The mechanism of action of dimethyl fumarate (abbreviated to DMF) addresses MS pathogenesis on multiple levels demonstrating anti-inflammatory and immunomodulatory properties. Both DMF and its primary metabolite monomethyl fumarate (MMF) significantly reduce immune cell activation and subsequent release of pro-inflammatory cytokines in response to inflammatory stimuli and also affect lymphocyte phenotypes through a down-regulation of pro-inflammatory cytokine profiles (T_H1, T_H17) and biases towards anti-inflammatory production (T_H2). DMF also appears to promote improvement in blood brain barrier integrity.

Other oral agents approved for treatment of relapsing forms of MS are fingolimod (Gilenya) and teriflunomide (Aubagio). Another oral immunomodifier, cladribine (Movectro) was approved in August 2010 for Relapsing Remitting Multiple Sclerosis (RRMS) only and only for up to 2 years but was subsequently withdrawn from the market by the sponsor. Other immunomodifier agents for MS include: interferon beta-1a, interferon beta-1b, glatiramer and natalizumab. Fampridine, is an orally administered non-disease modifying medication for MS. It was approved in Australia in May 2011 for the symptomatic improvement of walking ability in adult patients with MS who have shown improvement after 8 weeks of treatment.

The interferons and glatiramer have indications that include treatment after a single demyelinating event with associated brain magnetic resonance imaging (MRI) abnormalities characteristic of MS. Natalizumab is indicated only for treatment of RRMS. Interferon β-1b and natalizumab have indications which include delaying progression of disease/disability and reduction in frequency of relapse.

The precise mechanism of action of dimethyl fumarate (DMF) in MS is unclear. The sponsor claims that pharmacodynamic effects appear to be predominately mediated through activation of the nuclear factor (erythroid-derived 2)-related factor 2 (Nrf2) antioxidant response pathway, which is the primary cellular defence system for responding to a variety of potentially toxic stimuli. It may also have an immunomodulatory or anti-inflammatory action. In a variety of animal models, including collagen-induced arthritis and experimental autoimmune encephalitis, DMF was observed to reduce cytokine production and inflammation. Experimental autoimmune encephalitis is an animal model of antigen-induced central nervous system (CNS) inflammation that has many parallels with MS. Efficacy in that setting suggested that a similar benefit might be achieved in humans with MS.

The sponsor initially requested an indication for all forms of relapsing MS. As noted in discussions of recent submissions concerning MS, the McDonald's criteria for diagnosis of MS were amended in 2010. Patients with a single clinical episode and evidence of past demylination on MRI are now regarded as having clinically definite MS.

The *Guideline on clinical investigation of Medicinal Products for the Treatment of Multiple Sclerosis* provides the following advice on primary efficacy parameters in clinical trials for RRMS:

- The most relevant parameter in MS, the accumulation of disability, usually takes place over many years.
- Changes in progression of disability in a few years, which can be shown in clinical trials, could be accepted as a proof of efficacy, although it would be highly desirable to evaluate if the effect is maintained on a long-term basis.

- Changes in progression of disability should be distinguished between accumulation of disability in relation to relapses in Relapsing Remitting Multiple Sclerosis (RRMS) and progression of disability in Secondary Progressive Multiple Sclerosis (SPMS) or in Primary Progressive Multiple Sclerosis (PPMS).
- In patients with RRMS or SPMS with superimposed relapses (RMS), the primary efficacy parameter may also be the relapse rate although the number, duration or severity of relapses cannot be taken as a surrogate for disease progression and this would be expressed accordingly in the EU Summary of Product Characteristics (SmPC) (Product information in Australia).
- Progression of disability should be evaluated and worsening of disability should be reasonably excluded by means of adequately powered long-term studies.

Regulatory status

At the time of submission dimethyl fumarate (DMF) did not have marketing approval in any country but similar applications had been lodged in the European Union under the Centralised Procedure, the USA, Switzerland and Canada. DMF has subsequently been approved for marketing in Canada with an indication for RRMS and the USA with an indication for relapsing forms of MS (see Table 1 below).

Table 1. International regulatory status

United States of America	27 February 2012	Approved 27 March 2013	**TECFIDERA** is indicated for the treatment of patients with relapsing forms of multiple sclerosis
Canada	10 April 2012	Approved 03 April 2013	**TECFIDERA** is indicated as monotherapy for the treatment of relapsing remitting multiple sclerosis (MS) to reduce the frequency of clinical exacerbations and to delay the progression of disability

Product Information

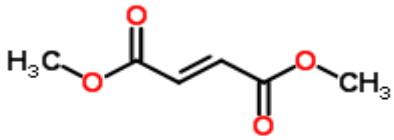
The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

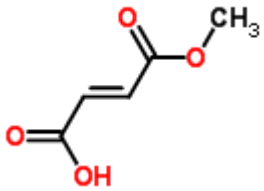
Drug substance (active ingredient)

Both DMF and Monomethyl Fumarate (MMF) (structures reproduced below) are achiral. The substance proposed for registration is the (*E*)-isomer, and is manufactured by chemical synthesis.

Figure 1. Chemical structures of DMF and MMF



Dimethyl Fumarate (CAS No 624-49-7)



Monomethyl Fumarate (CAS No 2756-87-8)

Only a single polymorph or pseudopolymorph has been described in the literature. The applicant has claimed that the drug is BCS Class 1.[2] Technically, this is not the case; although "highly soluble" across the pH range 4.0 – 8.0, dimethyl fumarate is acid labile. Further, no evidence was provided to support the implicit claim that the substance is also "highly permeable"; however, the literature[3] reports that of a series of homologous fumarates DMF showed the highest permeability in the Caco-2 cell model. However, in permeation experiments with intestinal mucosa in Ussing-type chambers, no undegraded DMF was found on the receiver side, indicating complete metabolism in the intestinal tissue.

Dimethyl fumarate does not have any ionisable group; therefore, no pKa was determined.

Only two impurities have been found in the drug substance: MMF and fumaric acid. Both are human metabolites and are adequately controlled in the active pharmaceutical ingredient (API) specification.

Drug product

The drug products are enteric coated microtablets encapsulated in hard gelatin capsule, and containing dimethyl fumarate 120 mg or 240 mg. A gastro resistant dosage form was necessary due to the acid lability of DMF.

The 120 mg capsule has a white body and green cap whereas the 240 mg capsule has a green body and green cap.

The formulation of the 240 mg product (which was developed after the 120 mg capsule) is different to that of the 120 mg product.

The US FDA Office of Generic Drugs[4] has not recommended any specific dissolution test method conditions for this product. The chosen method closely resembles Method B for delayed release dosage forms as described in USP <711>.

A shelf life of 36 months stored below 30°C has been allocated to the 120 mg capsule on a risk management basis; however, the limited data only support a shelf life of 9 months stored below 30°C for the 240 mg capsule. Although a tighter lower *Assay* limit has not been applied at batch release to accommodate decreases in active content observed during stability trials of the capsules, the 36 months shelf life has allocated on the grounds that:

[2] The Biopharmaceutics Classification System (BCS) is a guidance for predicting the intestinal drug absorption provided by the U.S. Food and Drug Administration. According to the BCS, drug substances are classified as follows: Class I: high permeability, high solubility; Class II: high permeability, low solubility; Class III: low permeability, high solubility; Class IV: low permeability, low solubility.
[3] Werenberg, D R *et al; Biopharm Drug Dispos*. 24(6), (2003), pp 259 - 273
[4] US FDA Office of Generic Drugs; *Dissolution Methods Database* at <http://www.fda.gov/cder/ogd/index.htm>

- The company could have applied expiry limits of 92.5 – 107.5% label claim (LC) in line with TGO 78[5] instead of the proposed (common release and expiry limits of) 95.0–105.0% LC, and these would have been accepted.
- The only degradants formed (fumaric acid and MMF) are human metabolites.

It follows that an active content of 92.5% LC would pose no safety concern to the patient, leaving all risk with the company in the event of the capsules being tested for regulatory purposes at some future time.

1. Acceptable release and expiry specifications have not been submitted for the finished products; instead, *"has been revised to ensure that it is clear that all acceptance criteria be met throughout the shelf life of the product, even if only tested at release"*, with the "formal" specifications to be submitted after approval of the changes proposed in the revised Module 3.2.P.5.1. This was accepted as an *interim measure*.

The limits proposed for the 2 identified impurities controlled in the finished product specifications have also been accepted on the grounds that each is a human metabolite.

Biopharmaceutics

DMF is rapidly hydrolysed to the active monomethyl fumarate (MMF). As the parent drug is undetectable in human blood or plasma, the outcomes of all supportive bioavailability/bioequivalence studies have been determined on the basis of MMF concentrations.

Study 109-HV-105 determined the pharmacokinetics of dimethyl fumarate and assessed the relative bioavailability of MMF from 2 of the 120 mg dimethyl fumarate capsules in comparison with a single dose of 240 mg of dimethyl fumarate API encapsulated in a hard gelatin capsule. As anticipated, the encapsulated active pharmaceutical ingredient (API) had a shorter lag time (T_{lag}), shorter time to peak plasma concentration (T_{max}) and a lower peak plasma concentration (C_{max}) compared to the encapsulated microtablets, which was attributed to the enteric coating. However, the PK profiles from both Treatments displayed high variability.

The following outcomes were obtained:

Table 2. Pharmacokinetic analysis for study 109HV105

	Arithmetic Mean	SD	Geometric Mean (a)	Geometric Mean Ratio (b)	90% CI of Geometric Mean Ratio (c)
N=12					
$AUC_{(0-inf)}$ (h*ng/mL)					
Standard Formulation	3137.8	741.04	3066.40	97.4%	(84.8%, 112.0%)
BG00012 API	3060.1	703.78	2987.87		
C_{max} (ng/mL)					
Standard Formulation	1790.0	312.35	1763.77		
BG00012 API	1435.8	1007.72	1237.50	70.2%	(51.9%, 94.8%)

NOTE: The analyses are based on the subjects having values in both periods. Twelve subjects completed periods 1 and 2 and received both treatments. Subject 103-008 received BG00012 API in period 1, but discontinued prior to dosing in period 2. Subject 103-011 received BG00012 Standard Formulation in period 1, and also discontinued prior to dosing in period 2.
(a) Antilog of least squares mean estimate from crossover analysis of variance model.
(b) Ratio of API/Standard Formulation.
(c) The normality assumption was valid, so the confidence intervals were constructed via the classical (shortest) confidence interval approach.

[5] Therapeutic Goods Order 78: This Order supersedes Therapeutic Goods Order No. 56 - General standard for tablets, pills and capsules, made on 19 September 1996 to introduce changes sought by the industry sectors to modernise requirements relating to the quality of tablets (but not including pills) and capsules, and is largely consistent with international standards, where such exist.

Study 109-HV-107 assessed the relative bioavailability of MMF from 2 of the 120 mg dimethyl fumarate capsules in comparison with a single 240 mg capsule under fasted conditions, and determined that exposure from both Treatments (results reproduced below) was similar in terms of C_{max} and AUC.

Table 3. Summary of bioequivalence analysis for plasma pharmacokinetic (PK) parameters. PK population. Study 109HV107.

	Arithmetic Mean	SD	Geometric Mean (a)	Geometric Mean Ratio (b)	90% CI of Geometric Mean Ratio (c)
N= 77					
$AUC_{(0-inf)}$ (h*µg/L)					
Two 120 mg BG00012 capsules	3866.2	1235.7	3689.9	1.03	(0.99, 1.07)
One 240 mg BG00012 capsule	3949.0	1146.3	3793.5		
C_{max} (µg/L)					
Two 120 mg BG00012 capsules	2339.9	1125.0	2099.8	1.06	(0.96, 1.16)
One 240 mg BG00012 capsule	2401.9	958.5	2222.7		

NOTE: The analyses are based on the subjects having values in both periods.
(a) Antilog of least squares mean estimate from crossover analysis of variance model.
(b) Ratio of test formulation/reference formulation.
(c) Confidence intervals were constructed via the classical (shortest) confidence interval approach.

Two studies were conducted to assess the effect of food: Study FAG-201-FGPK-02/02 was a preliminary investigation that appeared to not follow the FDA recommended design for food interaction studies in relation to subject numbers and meal design, whilst Study C-1903 was the definitive food effect study that assessed the effects of a high fat meal on drug bioavailability relative to the fasted state following administration of 2x120 mg of the proposed commercial formulation for Australia.

The following outcomes were reported:

Table 4. Monomethyl fumarate - treatment A versus B (fasting versus fed)

	T_{max} (h)	**C_{max} (ng/mL)**	**$AUC_{(0-\infty)}$ (ng.h/mL)**
A: Fasting	2.00	2.26	3.93
B: Fed	5.50	1.45	3.82
Statistical analysis:	**median diff**	**ratio (%)**	**ratio (%)**
A *versus* B Estimate	3.50	161.5	102.9
90% Confidence interval	-	(141 – 182)	(96 – 110)

Thus, for dimethyl fumarate and its metabolite, the extent of exposure (area under the plasma concentration time curve from time 0 to infinity ($AUC_{0-\infty}$)), but not the peak exposure (C_{max}), was equivalent in the fed state compared to the fasted state. Consumption of a high-fat meal led to a delayed T_{max} of 3.5 h and a 36% reduction in C_{max}, with respect to the MMF metabolite. No mention of these results is made in the draft Product Information leaflet.

Advisory committee considerations

Pharmaceutical sub-committee to the Advisory Committee on Prescription Medicines (ACPM)

Recommendation number 2315

1. The PSC endorsed all the questions raised by the TGA in relation to the quality and pharmaceutic aspects of the submission by Biogen Idec Australia Pty Ltd to register Tecfidera modified release capsule containing 120 mg and 240 mg of dimethyl fumarate.
2. The PSC agreed that the sponsor should address the issues relating to reprocessing of non-compliant batches to the satisfaction of the TGA.
3. The PSC advised that the sponsor should ensure that the drug substance manufactured at all nominated manufacturing sites are included in the batch analyses and stability trial protocols for the drug product.

   In the Product Information (PI) the "*Description*" section should be amended to include the partition coefficient and solubility of the drug substance at relevant physiological pH.

There was no requirement for this submission to be reviewed again by the PSC before consideration by the ACPM.

Quality summary and conclusions

A number of questions have been raised with the sponsor concerning the quality/biopharmaceutical data, to which satisfactory responses were provided.

Approval was recommended from a quality/biopharmaceutic perspective.

III. Nonclinical findings

Introduction

An adequate set of nonclinical studies was submitted, with relevant studies being Good Laboratory practice (GLP) compliant, with the exception of the *in vivo* cardiovascular/respiratory safety pharmacology study in dogs.

Pharmacology

Primary pharmacology

Mode of action

Multiple sclerosis (MS) is a chronic autoimmune and neurodegenerative disorder of the central nervous system (CNS) that is characterised by inflammation, demyelination, and oligodendrocyte and neuronal loss. Oxidative stress associated with reactive oxygen and nitrogen species is implicated as a significant factor in the pathology of MS.[6] The post-

[6] Gilgun-Sherki, Y., Melamed, E. and Offen. D. (2004) The role of oxidative stress in the pathogenesis of multiple sclerosis: the need for effective antioxidant therapy. J. Neurol. 251, 261-268.

mitotic cells in the CNS have a low capacity for mitigating oxidative stress and are susceptible to its damaging effects.[7]

Primary pharmacology studies revealed that dimethyl fumarate (DMF) has anti-inflammatory and neuroprotective activity (see below). Evidence was provided that DMF activates the Nrf2 antioxidant response pathway and may exert its effects, at least in part, via this mechanism. Nrf2 is a transcription factor that controls the expression of various genes, including those whose protein products are involved in the detoxification and elimination of reactive oxidants, thus allowing cells to respond to various forms of oxidative stress.[8] It is well established that Nrf2 activity is controlled, in part, by the cytosolic protein, kelch-like ECH-associated protein 1 (Keap1). Under basal conditions, Nrf2 is anchored in the cytoplasm through binding with Keap1 which results in its ubiquination and subsequent proteosomal degradation. Mass spectrophotometric analysis revealed that both DMF and its primary metabolite, monomethyl fumarate (MMF), cause molecular changes to rat Keap1 within a peptide fragment including the critical Cys-151, indicating that they can both alkylate the reactive thiol. This would be expected to result in a reduction in binding of Keap1 to Nrf2 and an increase in steady-state Nrf2 protein levels, and the latter was demonstrated in cell lysates/extracts from various cell types, including human astrocytes (the CNS cells that regulate the myelinating activity of oligodendrocytes, amongst other functions), treated with DMF and/or MMF, and the effect was concentration dependent.

To have an effect on gene expression, Nrf2 needs to be translocated from the cytoplasm to the nucleus, and such translocation was demonstrated in DLD-1 cells (a colonic epithelial cell line) treated with DMF, and human astrocytes treated with DMF and MMF. In the nucleus, Nrf2 binds to a specific promoter sequence known as the Antioxidant Response Element (ARE). The ARE regulates expression of antioxidant and stress response-associated genes, with transcription of these genes initiated when Nrf2 binds to it. DMF and MMF treatment of an ARE reporter cell line resulted in up-regulated transcription (luminescence). DMF and/or MMF were also demonstrated to up-regulate transcription of several endogenous Nrf2 target genes in various cell types, including human and rat astrocytes and oligodendrocyte precursor cells and human hippocampal neurons. Through experiments using siRNA constructs in DLD-1 cells, the up-regulation of target genes was shown to be at least partially dependent on Nrf2.

Up-regulation of NAD(P)H dehydrogenase (quinone 1)(NQO1) and aldo-keto reductase 1B8 (AKR1B8) (marker genes) was demonstrated in mice *in vivo* in response to DMF. Different organs showed quantitative differences in the up-regulation of the two genes, suggesting some tissue specificity of response. Rats showed a similar pharmacological response to mice and MMF had similar activity to DMF. An essential role of Nrf2 in the up-regulation was confirmed using Nfr2 knockout (KO) mice (Nrf2-/-).

Up-regulation of NQO1 and AKR1B8 genes in tissues from the CNS was quantitatively small (see Table 5 below). At a dose of 200 mg/kg that was required to see even a small effect on target gene up-regulation in the brain, the animal: human exposure ratio (ER) was about 4 in mice and 3 in rats (ER values were from the repeat dose toxicity studies, although the strains of rats used were different).

[7] Scannevin, R.H., Chollate, S., Jung, M., Patel, H., Bista, P., Zeng, W., Ryan, S., Yamamoto, M., Lukashev, M. and Rhodes, K.J. (2012) Fumarates promote cytoprotection of central nervous system cells against oxidative stress via the nuclear factor (erythroid-derived 2)-like 2 pathway. J. Pharmacol. & Exp. Therap. 341, 274-284.
[8] Lau, A., Villeneuve, N.F., Sun, Z., Wong, P.K. and Zhang, D.D. (2008) Dual roles of Nrf2 in cancer. Pharmacol. Res. 58, 262-270.

Table 5. Up-regulation of NQO1 and AKR1B8 genes in tissues from the CNS.

Study	Species (strain)	Tissue	Dose (mg/kg)	Single dose/repeat dose	Fold upregulation of NQO1	Fold upregulation of AKR1B8
RSCH-2011-025	Mice (C57BL6)	Forebrain Cerebellum	200	Single	1.6 -	- -
		Forebrain Cerebellum	50		- -	- -
	Rats (Brown Norway)	Cerebellum	200		-	-
RSCH-2011-028	Mice (C57BL6)	Brain	200	Single	1.6 (significant)	NE
			50		-	NE
RSCH-2011-030	Rats (Brown Norway) with EAE	Spinal cord Cerebellum	200	Repeat	- -	- 3
		Spinal cord Cerebellum	100		- -	- -

- = no or minimal up-regulation observed (< ~1.5 fold); NE = not examined; again, the essential role of Nrf2 in the up-regulation was confirmed using KO mice which showed no up-regulation of NQO1 (in either brain or spleen)

Anti-inflammatory effects

The anti-inflammatory activity of DMF was demonstrated both *in vitro* and *in vivo*. *In vitro*, pretreatment with DMF reduced expression of pro-inflammatory cytokines in LPS-stimulated RAW264.7 and J774A.1 macrophages, in primary cultures of mouse bone marrow derived macrophages (BMDM) and in rat astrocytes (Study RSCH-2011-023). Comparing effects of DMF in BMDM from wild type and Nrf2 knockout mice suggested that Nf2 contributes to, but is not required for, the suppression of LPS-induced stimulation of IL-1β and IL-10. Thus, DMF may therefore be working through Nrf2 independent mechanisms, as well as Nrf2 dependent mechanisms.

It is difficult to make comparisons between drug concentrations expected in the clinic and those that were active in cells *in vitro* (Study RSCH-2011-023) because clinical data are for MMF (although similar activity of DMF and MMF can be assumed), no statistical analysis was conducted in the study, the concentrations at which DMF showed substantial activity varied with the cell type and the cytokine, and data for MMF concentrations in the CNS were limited. In general, substantial activity of DMF was observed at 10 µM which is below

the expected C_{max} of MMF (~2 µg/mL (Clinical Study 109MS101) or ~15 µM) at the maximum recommended human dose (MRHD). However, data from Study RSCH-201-027 revealed that brain and spinal cord MMF concentrations were only approximately 8% and 22% of plasma concentrations (at 30 min post dose in rats), suggesting respective brain and spinal cord concentrations of ~1 and 3 µM in patients given the MRHD. Some anti-inflammatory activity of DMF at concentrations of ~1-3 µM was observed.

In vivo, DMF was active in animal models of inflammation. In the collagen-induced rat arthritis model, DMF at 200 mg/kg/day PO reduced arthritic paw inflammation, and delayed pro-inflammatory cytokine production and the expression of myeloid markers in the paw. In rat experimental autoimmune encephalomyelitis (EAE), an inflammatory demyelinating disease of the CNS that is widely used as a model of human CNS demyelinating diseases such as MS, 100 mg/kg/day DMF PO reduced clinical signs of disease, while 200 mg/kg/day eliminated them. In spinal cord, markers of inflammation, IBA-1 (marker of macrophage/microglia activation) and CD3 (marker of T cell activation), were both reduced at DMF doses ≥25 mg/kg/day, and expression of genes for pro-inflammatory cytokines was decreased in a dose-dependent manner (over 5-100 mg/kg/day). Up-regulation of Nrf2 target genes, NOQ1 and AKR1B8, in EAE rats was similar to that seen in healthy rats (at least in the tissues examined in both). However, the role of Nrf2 activation in the anti-inflammatory activities in these two rat models is not clear. The 200 mg/kg/day dose of DMF (the only dose tested in the arthritis model and the dose showing elimination of clinical symptoms in the EAE model) was slightly higher than the human dose (~3 fold based on plasma AUC for a different strain, or ~5 fold based on body surface area (mg/m^2)), but some anti-inflammatory activity *in vivo* was observed at lower doses.

Neuroprotective effects

Neuroprotective activity of DMF and/or MMF was demonstrated *in vitro* and *in vivo*. *In vitro*, increases in Nrf2 levels and up-regulation of NQO1 were observed in primary cultures of several CNS cell types, including human astrocytes and hippocampal neurons, and human and rat oligodendrocyte precursor cells. Cytoprotection of human astrocytes and rat embryo cortical neurons from oxidative stress (challenge with hydrogen peroxide (H_2O_2)) was demonstrated by an improvement in various markers of cell viability and reversal of intracellular calcium accumulation. A potential mechanism for this cytoprotective effect was via increased cellular levels of glutathione. The essential role of Nrf2 in this cytoprotective effect of DMF/MMF was demonstrated in human astrocytes transfected with Nrf2 siRNA in which the protective effect of MMF from H_2O_2 challenge was obliterated.

Concentrations at which DMF and MMF showed at least some cytoprotection of cultured human astrocytes from H_2O_2 challenge were ≥0.4 µM, although no statistical analysis was conducted for the astrocyte experiments. In rat cortical neurons, 3.3 µM showed significant cytoprotection from H_2O_2 challenge but lower concentrations were not tested. In patients at the MRHD, brain and spinal cord MMF concentrations might be expected to be about 1-3 µM which is of the same order of magnitude of concentrations found to show some cytoprotection *in vitro*.

Direct neuroprotective effects were investigated in the rat using the malonate neurotoxicity model which has little inflammatory component. Malonate inhibits the mitochondrial enzyme succinate dehydrogenase which results in destabilisation of mitochondrial function; neurons are rendered susceptible to oxidative stress and degenerate leading to an intra-striatal lesion.[9] Rats given DMF (75 and 100 mg/kg PO) had significant (up to 61%) reductions in malonate-induced lesion volume. The 100 mg/kg

[9]Fancellu *et al*. (2003) Neuroprotective effects mediated by dopamine receptor agonists against malonate-induced lesion in the rat striatum. Neuro. Sci. 24, 180-181.

dose resulted in a significant improvement in apomorphine-induced rotational behavioural responses, and an increase in the number of surviving neurons in the lesion as revealed by neuron-specific immunostaining.

Efficacy indicative of neuroprotection was achieved in the EAE model (reduced demyelination and cell degeneration in the spinal cord, and improved motor function) and in malonate-induced striatal lesions at a dose 100 mg/kg and 75 mg/kg, respectively (that is, at exposures similar to, or a little higher than, the proposed clinical dose).

Secondary pharmacodynamics and safety pharmacology

No secondary pharmacology studies were submitted. Clinical experience has identified flushing as a side effect of DMF treatment, but clinical rather than nonclinical studies were conducted to investigate the mechanism for this effect.

Specialised safety pharmacology studies covered the cardiovascular and respiratory systems. In *in vitro* studies, no effects of DMF or MMF were observed on potassium hERG currents in stably transfected human embryonic kidney cell line (HEK293) or on action potential duration (from the midpoint of the upstroke to 60% or 90% repolarisation (APD_{60} or APD_{90})) in canine Purkinje fibres at concentrations (both compounds) of up to 1500 µM. At the MRHD, C_{max} was approximately 15 µM, so the 1500 µM concentration of MMF corresponds to approximately 100 fold the expected clinical C_{max}. The *in vivo* cardiovascular/ respiratory study in dogs, using doses of 10-1000 mg/kg PO, achieved C_{max} values of 5.04-47.7 µg/mL, about 2.5-24 fold the expected clinical C_{max}. Effects observed (increases in heart rate and decreases in blood pressure) were not clearly dose related and were confounded with the stress of vomiting. Effects on blood pressure were quantitatively minor and there were no effects on electrocardiogram (ECG). ECG data from several repeat dose toxicity studies (4 weeks and 11 months in dogs and 12 months in cynomolgus monkey) did not reveal any clear positive findings.

Safety pharmacology studies examining effects on the CNS were limited to 4 studies conducted in mice with orally-administered Fumaderm (a mixture of DMF and monoethyl fumarate salts), as reported in the sponsor's Pharmacology Written Summary. Although no effects were observed, these studies had the following limitations: (i) full data were not supplied; (ii) only a limited set of end points (body temperature, mobility, nociceptive behaviour, sleeping time) were examined; (iii) the studies were not conducted specifically with DMF or MMF; (iv) doses were low and there were no PK or toxicokinetic data (the highest dose tested was 464 mg Fumaderm/kg, which corresponds to a dose of 259.8 mg/kg (780 mg/m^2), given that 56% of the total fumarate content of Fumaderm is DMF; the human dose is 480 mg corresponding to 6.857 mg/kg (254 mg/m^2) for a 70 kg person, giving an ER of 3 (calculation assumes comparable absorption of DMF from Fumaderm and the commercial DMF formulation). There was little evidence of CNS toxicity in the repeat dose toxicity studies, although some CNS type clinical signs (for example, ataxia, tremors and convulsions) were observed in the acute studies in rats and mice at high doses.

The pharmacological properties did not raise any other issues requiring further investigation in specialised safety pharmacology studies.

Pharmacokinetics

Absorption

Absorption data after a single dose of DMF were limited, and largely provided by older studies, although pharmacokinetic data were available from a study in dogs after administration of the formulation proposed for registration (enteric coated microtablets

in gelatin capsules). Oral DMF was 100% absorbed in the rat as revealed by comparison of AUC for radioactivity after oral and IV administration.

Data from all studies indicated that DMF is completely metabolised presystemically as it was not found as a circulating entity in any study in which plasma DMF concentrations were measured, including the dog study in which DMF was administered directly into sites within the small intestine and colon. It was also not found when plasma was radiochromatographed after oral administration of radioactively labelled (^{14}C)-DMF to rats. These results are consistent with literature data from an *in vitro* study[10] which revealed that DMF was rapidly metabolised by esterases in intestinal perfusate and homogenate.

DMF is metabolised to MMF, and this metabolite which is also pharmacologically active, was measured in plasma in order to estimate exposure in the animal species used in the toxicity studies and to make comparisons with humans. Exposure was confirmed in all the repeat dose toxicity studies and the majority of these studies, as well as the carcinogenicity studies, were supported by good quality toxicokinetic data.

MMF was rapidly absorbed after oral administration, with plasma MMF T_{max} generally being 10 min in mice, 15-30 min in rats, 20 min to 1 h in cynomolgus monkeys, 30 min to 4 h in dogs and 2-2.5 h in humans. Plasma T_{max} for radioactivity after oral administration of ^{14}C-DMF in rats was also 30 min. Plasma AUC and C_{max} values were broadly dose proportional in dogs given the proposed commercial formulation (single dose) and in all species investigated in repeat dose studies except at higher doses in dogs when vomiting interfered with absorption. Dose proportionality of exposure was also observed in humans. There did not appear to be any gender differences in AUC values in mice, dogs or cynomolgus monkeys. In rats, females tended to have slightly higher AUC values than males. There was little or no evidence of accumulation with repeated dosing in any of the laboratory species investigated, or in humans. Terminal half life of MMF was short in all species (about 1 h in rats, dogs and humans).

The proposed commercial formulation is an enteric coated formulation and a study was conducted in dogs that revealed comparable exposure to MMF when drug was absorbed from any region of the small intestine (duodenum, jejunum or ileum). A study was also conducted in dogs to investigate the possibility of using sustained release formulations to allow less frequent dosing. Compared to the proposed commercial formulation, the sustained release formulations had longer T_{max} values (3-4 h versus 1 h) and $t_{1/2}$ values (1-4 h versus 0.5 h) and reduced C_{max} values (0.5-1 µg/mL versus 6 µg/mL) and $AUC_{0-\infty}$ values (3-5 ng.h/mL versus 8 ng.h/mL). The sponsor concluded that the commercial formulation had more appropriate pharmacokinetic properties than the various sustained release formulations.

Distribution

Plasma protein binding of MMF as determined by equilibrium dialysis was low in all species investigated, but particularly the laboratory animal species (0% in rats, 2.8% in monkeys (presumably cynomolgus), 23% in dogs and 40% in humans), and was independent of drug concentration over the range 0.05-5 µM (although this range does not cover the expected clinical C_{max} at the MRHD, ~15 µM). A slightly lower extent of protein binding (28%) was estimated for human plasma using ultrafiltration, with binding again being independent of drug concentration over the smaller range of 1.25-10 µg/mL covering the clinical C_{max}. Exposure ratios in this report have not been corrected for species differences in protein binding because correction would mean relatively small

[10]Werdenberg, D., Joshi, R., Wolffram, S., Merkle, H.P. and Langguth, P. (2003) Presystemic metabolism and intestinal absorption of antipsoriatic fumaric acid esters. Biopharmaceutics & Drug Disp. 24, 259-273.

changes (≤40%). Plasma protein binding (human) of MMF appeared to be mainly due to human serum albumin with little binding to alpha 1-acid glycoprotein observed.

Distribution (and metabolism) of orally administered ^{14}C-DMF was investigated in the rat, with the Long Evans strain being used rather than the Sprague Dawley strain (which was used in toxicity studies), presumably because it is pigmented (allowing investigation of melanin binding). DMF metabolites were extensively and rapidly distributed to tissues, with T_{max} values for radioactivity in the majority of tissues being 30 min, the same as for plasma. There was no evidence of melanin binding in either of two studies in Long Evans rats. The large volume of distribution estimated in dogs given the commercial formulation proposed for registration (V_z/F, ~1-2 L/kg) is consistent with the extensive tissue distribution observed in rats. This volume of distribution in the dog was similar to clinical values for MMF which was in the range 60-90 L (about 1 L/kg). The liver, stomach and kidney had the highest concentrations of radioactivity at the time of peak tissue concentrations (30 min), presumably reflecting the liver as the major organ of metabolism and the kidney as a major organ of excretion. However, by 30 min post dose, a large proportion of radioactivity was present as glucose rather than MMF, which would explain the high ratio of brain: plasma concentrations of radioactivity. There were no apparent sex differences in tissue distribution. There was no evidence of retention of radioactivity in any specific tissue. However, radioactivity was eliminated more slowly from tissues than from plasma, and concentrations of radioactivity in tissues at 72 h post dose were still sizeable, probably reflecting radioactivity incorporated into normal intermediary metabolism.

MMF was not found to preferentially partition into the cellular components of blood (whole blood: plasma concentration ratios were <1 over the range 0.05-5 μM), but total radioactivity was present in higher concentrations in blood than plasma (AUC ratio 2.1) suggesting an affinity of metabolites for the cellular components of blood.

Study RSCH-2011-027 revealed the distribution of MMF into the CNS (brain and spinal cord).

Metabolism

After oral administration of ^{14}C-DMF in the Long Evans rat, there were no apparent gender differences. DMF was extensively metabolised, with less than 0.2% of the dose excreted in 0-48 h urine as unchanged drug (little radioactivity was excreted in faeces). MMF was also extensively metabolised (MMF in 0-48 h urine was only 1.13% of the dose). The major metabolites identified in urine were the N-acetylcysteine conjugates of monomethyl- and dimethyl-succinate and cysteine conjugates of monomethyl succinate. Together, these metabolites in 0-48 h urine represented 10.7% of the administered dose. Similar results were obtained in humans, with little DMF excreted in urine (<0.1% of radioactivity in 0-48 h urine; little radioactivity was excreted in faeces), and extensive metabolism of MMF (MMF represented 0.23% of radioactivity in 0-48 h urine). Human urine contained the same metabolites as rat urine, although the cysteine conjugates were predominant in humans as opposed to the N-acetylcysteine conjugates in rats.

Glucose was the main circulating metabolite, followed by fumaric acid (FA) + citric acid (CA), in both rats and humans. Glucose accounted for 48.2% of total extractable plasma radioactivity ($AUC_{0\text{-}72\,h}$), FA + CA for 32.4% and MMF for 0.19% in rats. Results were similar in humans. N-acetylcysteine conjugates of monomethyl succinate were also identified in rat plasma (not human plasma) but only comprised a small proportion of total circulating radioactivity.

The role of the TCA cycle in the metabolism of fumarate is well established in the literature and the results for metabolism of orally administered ^{14}C-DMF in rats and humans were consistent with this knowledge. The large proportion of the administered dose recovered

in expired air in both rats and humans is indicative of complete metabolism of ^{14}C-DMF to radioactively labelled carbon dioxide ($^{14}CO_2$). The proposed metabolic pathways for DMF would be the same for all species. Given the species conservation of these pathways, it is acceptable that metabolism studies were not conducted in the other species used in the repeat dose toxicity studies.

In early studies with unlabelled drug, plasma FA concentrations did not rise above endogenous levels in dogs given a single oral dose of 16.7 mg/kg DMF, while in rats given the same dose, plasma FA concentrations were slightly higher in samples over 0.25-2 h compared with 4 h (a pre-dose value was not available). These data suggest that CA comprised the majority of the combined FA + CA peak in plasma.

While MMF was much more stable in plasma than DMF, it was rapidly metabolised after oral administration of ^{14}C-DMF in the rat, with only 2.66% of plasma radioactivity present as MMF at 0.5 h. The excretion of 44-50% of the radiolabelled dose into expired air within 4 h of oral or intravenous (IV) administration reveals the rapidity of metabolism to CO_2. MMF was not metabolised by human liver microsomes or by recombinant human cytochromes, CYP2D6 and CYP3A4.

Radioactivity was eliminated from plasma considerably more slowly than MMF in rats ($t_{1/2}$ of radioactivity was about 42 h compared to about 1 h for MMF), suggesting slow elimination of some metabolites, which would be consistent with radioactivity incorporated into normal intermediary metabolites.

Excretion

As noted above, excretion in rats after an oral dose of about 10 mg/kg ^{14}C-DMF was predominantly via expired air (61-66% of the dose over 96 h in 2 experiments), with renal excretion also being substantial (21-23% of the dose), but faecal excretion being relatively minor (2.9-3.6% of the dose). Similar proportions were observed in humans, about 40-59% in expired air over 0-96 h, and 16% in urine and less than 1% in faeces over 0-168 h.

Conclusion

The metabolic routes via esterases and the enzymes involved in the TCA cycle are the same for humans and the laboratory animal species, therefore all the species used in the toxicity studies, including those used in the pivot repeat dose toxicity studies, serve as appropriate models for the assessment of DMF/MMF toxicity in humans.

Pharmacokinetic drug interactions

Four cytochrome P450 (CYP) enzyme inhibition studies, all including positive controls, were conducted testing DMF and MMF (3 studies) or MMF only (1 study). Maximum concentrations tested were 50-300 µM (approximately 3-20 fold the expected C_{max} at the MRHD) and CYP isozymes investigated were CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4. There were no consistent findings revealing any CYP enzyme inhibition that would be of clinical relevance.

Two *in vitro* enzyme induction studies were conducted testing MMF at concentrations up to 100 or 200 µM (approximately 7-13 fold the expected C_{max} at the MRHD) in primary cultures of human hepatocytes. If the criteria for a positive response are a greater than 2 fold induction compared to the vehicle and an induction which is at least 40% of the positive control[11], then all responses in both studies were outside these limits, suggesting

[11]Bjornsson, T.D., Callaghan, J.T., Einolf, H.J., Fischer, V., Gan, L., Grimm, S., Kao, J., King, S.P., Miwa, G., Ni L., Kumar, G., McLeod, J., Obach, R.S., Roberts, S., Roe, A., Shah, A., Snikeris, F., Sullivan, J.T., Tweedie, D., Vega, J.M.,

little potential for any clinically relevant enzyme induction. Major CYP enzymes were tested (CYP1A2, 2B6, 2C8, 2C9, 2C19 and 3A4), as well as P-glycoprotein.

In two studies, one in LLC-PK_1 cells and one in Caco-2 cells, neither DMF (up to 300 µM and 500 µM, respectively) and MMF (up to 300 µM and 50 µM, respectively) inhibited the transport of radioactive hydrogen labelled (^3H)-digoxin, suggesting no clinically relevant potential for pharmacokinetic drug interactions mediated by P-gp (positive controls showed the expected inhibition).

Toxicology

Acute toxicity

The acute toxicity of DMF given PO and intraperitoneally (IP) was investigated in rats and mice. The 50% lethal dose (LD_{50}) values and maximum non-lethal doses were high, the former being about 1000 mg/kg in mice (both routes) and in rats dosed IP, and about 3000 mg/kg in rats dosed PO. Gross necropsy findings were observed in the stomach and kidneys in both species, and in the liver in mice.

Repeat dose toxicity

Repeat dose toxicity studies, all using the clinical (oral) route, were conducted in mice (up to 3 months duration), rats (up to 6 months), dogs (up to 11 months) and cynomolgus monkeys (up to 12 months). As noted above, these species are all considered appropriate models for humans based on the same metabolic pathways in all species. All pivotal studies were GLP compliant and were supported by toxicokinetic data. Overall, studies were well designed and conducted; group sizes and parameters examined were adequate, dose levels were generally appropriate and in most studies, both sexes were investigated. The formulation used in the pivotal 11 month dog study (microtablets in gelatin capsules) was the commercial formulation.

The majority of the repeat dose toxicity studies employed once daily dosing (although the pivotal 11 month dog study was a notable exception), even though the frequency of dosing of MS patients is twice daily. The frequency of dosing can influence the results of toxicity studies but generally quantitatively rather than qualitatively. There were no studies that specifically investigated differences in toxicity between once and twice daily dosing, although two of the special studies investigating renal toxicity (the 2 week and 14 week studies) included comparisons of once and twice daily dosing. Similar renal toxicity of DMF was observed after once and twice daily dosing in the 2 week study, while slightly greater toxicity after once daily dosing was observed in the 14 week study.

Relative exposure

Exposure ratios have been calculated based on animal: human plasma MMF AUC values. Human reference values are from Clinical Study 109MS101 (see Table below).

Achieved exposure ratios were acceptable in the mouse (up to 9 in the 3 month study), moderate in the dog (up to 7 in the 11 month study) and monkey (up to 6 in the 12 month study) and low in the rat (up to 3 in the 6 month study) but maximum doses were limited by reduction in food consumption (mice, rats and monkeys) or emesis (dogs) and subsequent body weight loss/reduction in body weight gain. In the pivotal dog study, food consumption and body weight gain were markedly reduced at the high dose (HD) making

Walsh, J. and Wrighton, S.A. (2003) The conduct of *in vitro* and *in vivo* drug-drug interaction studies, A PhRMA perspective. J. Clin. Pharmacol. 43, 443-469.

it difficult to differentiate a direct effect of the drug from a secondary effect due to poor nutritional status, so the maximum ER was, in effect, 4.

Table 6. Relative exposure in repeat-dose toxicity and carcinogenicity studies

Species	Study duration	DMF dose (mg/kg/day)	MMF AUC_{0-t} (µg·h/mL)^	Exposure ratio#
Mouse (CD-1CD57BL/6)	4 weeks	50	14.5	1.8
		100	28.2	3
		250	88.5	11
		400	127	15
Mouse (CD-1)	3 months	50	5.9	0.7
		200	31.2	4
		400	77.0	9
	2 years [carcinogenicity]	25	3.0	0.4
		75	10.9	1.3
		200	35.4	4
		400	102.1	12
Rat (SD)	3 months	50	5.8	0.7
		100	11.1	1.3
		250	22.9	3
	3 months	50	7.7	0.9
		250 (cornstarch)	44.9	5
		250 (hypromellose)	43.1	5
	6 months	25	2.95	0.4
		100	14.8	1.8
		200	28.5	3
	2 years [carcinogenicity]	25	3.8	0.5
		50	8.9	1.1

Species	Study duration	DMF dose (mg/kg/day)	MMF AUC_{0-t} (µg·h/mL)^	Exposure ratio#
		100	16.5	2
		150	29.6	4
Dog (Beagle)	4 weeks	50	58.6*	7
		100	111.5*	14
	11 months	5	7.1	0.9
		25	30.7	4
		50	56.6	7
Monkey (Cynomolgus)	12 months	5	2.4	0.3
		25	13.7	1.7
		75	48.0	6
Human (MS patients; n=24)	Day 1	240 mg BID	8.205	–

^ $AUC_{0\text{-}24\,h}$ for humans and the pivotal dog and monkey studies (although these values should correspond closely to $AUC_{0\text{-}t}$); # = animal:human plasma MMF AUC; * calculated from day 14 and 28 data. BID=twice a day.

Major toxicities

Major target organs identified in the repeat dose studies were the non glandular stomach (mouse and rat), the kidney (rat, dog and monkey), testes (mouse and dog; also identified as a target organ in rats in the male fertility study) and the liver (rat).

In the 4 week study in dogs, changes were observed in other organs but were likely to have been associated with poor nutritional status subsequent to persistent postdose emesis and this study was followed by a more careful examination of the tolerability of the drug in this species to enable appropriate selection of doses for the pivotal 11 month study.

Stomach

In mice and rats, the non glandular stomach (forestomach) was the major target organ. In some of the study reports, it was not always clear whether histopathological changes were in the glandular or non glandular stomach, however, the vast majority of changes appeared to be in the non glandular portion. In the 3 month mouse study and in both the 3 month rat studies, the low dose (LD) of 50 mg/kg (ER approximately 0.7 in both species) caused non glandular stomach changes. Similarly, in the 6 month rat study, the LD of 25 mg/kg (ER 0.4) caused non glandular stomach changes. No Observable Adverse Effect Levels (NOAELs) were therefore not determined in any of these studies.

The main findings were increased stomach weight, and non glandular stomach hyperkeratosis, hyperplasia, inflammation, ulceration and cellular infiltration. Severity of findings ranged from that of minimal to marked. At least partial recovery was observed

over treatment-free periods. As this organ has no counterpart in humans, the non glandular stomach changes observed in rodents are unlikely to be of clinical relevance.

Few changes were observed in the glandular stomach (subacute inflammation in the 6 month rat study, as well as some changes in the rat carcinogenicity study, and submucosal mononuclear cell infiltration in the 4 week dog study). Further, the proposed formulation for registration is an enteric coated microtablet designed to release DMF in the intestine and therefore avoid local exposure of the stomach to the drug. There were no increases in stomach weight or histopatholgical changes in the stomach in the 11 month dog which used the enteric coated formulation; there were also no findings in the small intestine where drug would be released after administration of this formulation. There were also no histopathological findings in the stomach in the 12 month monkey study (and no increase in stomach weight). It is noted, however, that gastrointestinal disorders were common adverse events in the clinical studies.

While the oesophagus is morphologically similar to the non glandular stomach of rodents, there were no findings in the oesophagus in the pivotal dog and monkey studies, probably because of the rapid passage of drug through the oesophagus compared with the more prolonged exposure of the non glandular stomach in rodents.

Changes in the non glandular stomach probably contributed to the reduction in food consumption and subsequent reduction in body weight gain/loss of body weight following treatment in rodents.

Testes and epididymides

Changes in the testes were observed in mice, rats and dogs, but not in monkeys. The main findings were testicular tubular epithelial degeneration which was observed in the former 3 species and interstitial cell hyperplasia, progressing to neoplasia, which was observed in rats.

Testicular tubular epithelial degeneration was observed only at high exposures in mice. Thus, there were no histopathological findings (only reduced testes weight) in the 3 month study in CD-1 mice at doses up to 400 mg/kg/day (ER 9), while in the 4 week study, tubular degeneration was observed in BC57BL/6 strain mice at 400 mg/kg/day (ER 15) and in P53N5-W strain mice at 250 mg/kg/day (the only dose level tested in this strain; no toxicokinetic data, but ER 11 at the same dose in the BC57BL/6 strain). Also observed in this study, but not in the 3-month study in CD-1 mice, were the more minor findings of tubular hypocellularity (at ≥100 mg/kg/day in BC57BL/6 strain mice and at 250 mg/kg/day in P53N5-W strain mice) and sperm granuloma in the epididymides (at all doses (≥50 mg/kg/day) in BC57BL/6 strain mice and at 250 mg/kg/day in P53N5-W mice).

In rats, testicular tubular epithelial degeneration was only observed after prolonged dosing; it was not observed in the repeat dose studies up to 6 months but was seen in the carcinogenicity study (increased incidences at 100 and 150 mg/kg/day (ERs 2 and 4, respectively)). Interstitial hyperplasia, a finding only in rats, was also not consistently observed. Thus, it was not observed in the repeat dose studies (in the two 3 month studies, both at doses up to 250 mg/kg/day (ER 3-5), or in the 6 month study at doses up to 200 mg/kg/day (ER 3)), but was seen in the male fertility study (about 14 weeks duration) at relatively high incidence (9/25) at both 250 mg/kg/day (ER about 3-5) and 375 mg/kg/day (ER estimated as ~6). This study was in the same strain as the repeat dose studies but was conducted by a different laboratory. This finding was not associated with any reduction in fertility. Interstitial cell hyperplasia and an increased incidence of interstitial cell adenoma were also observed in the rat carcinogenicity study at doses ≥100 mg/kg/day (ER 2) (see discussion below).

In dogs, there were no testicular findings in the 4 week study but in the 11 month study testes weights were decreased and there was an increased incidence of tubular epithelial degeneration and spermatid giant cells at the HD (50 mg/kg/day, ER 7), associated with persistent emesis and poor nutritional status. Hypospermia in the epididymides was also observed at this dose.

In summary, the risk of testicular changes in the clinic is likely to be relatively low because testicular findings were not seen in monkeys and tubular degeneration was observed only at high ERs in mice, after prolonged dosing in rats and at high doses associated with poor nutritional status in dogs. Interstitial cell hyperplasia was observed only in rats, was not a consistent finding and was not associated with a reduction in fertility.

Liver

Liver weights were increased in a number of species (in mice (3 month study), in rats (both the 3 month and the 6 month studies), and monkeys (12 month study). In mice and monkeys, this may have reflected an adaptive change as there were no histopathological findings in the liver or increases in serum transaminases. However, the liver was identified as a target organ in the rat, with histopathological changes being observed in the 6 month and carcinogenicity studies, although not in the 3 month studies. The findings were different in these two studies, with necrosis (focal/multifocal) and bile duct hyperplasia observed in the 6 month study, mainly in females at ≥100 mg/kg/day (ER 1.8), and increased incidences of centrilobular vacuolation observed in the carcinogenicity study at ≥50 mg/kg/day (ER 1.1). In the 6 month study, maximum incidences of necrosis were 1/15 (7%) and 5/15 (33%) in males and females, respectively, and of bile duct hyperplasia were 1/15 (7%) and 8/15 (53%), respectively. These findings were observed at clinically relevant exposures but were of minimal severity, were not accompanied by any increase in serum transaminases, and showed some reversibility.

In summary, the toxicological effects of DMF on the liver appeared to be rat specific, with no changes observed in dogs and only increased liver weights observed in mice and monkeys. Increased serum transaminases were not observed in any of the laboratory species in the repeat dose toxicity studies.

Kidney

Increased kidney weights were observed in all species investigated in the repeat dose toxicity studies. In mice, kidney changes were limited to increases in kidney weight, while in rats, dogs and monkeys, several histopathological changes were also observed. Changes were dose dependent in all species and duration dependent (rat data). All changes were of minimal to mild severity in all species. Tubular epithelial regeneration was observed in all these species but other tubular changes differed between species: epithelial hypertrophy and vacuolation (rats and dogs), basophilia (this change is often associated with regeneration) and epithelial hyaline droplets (rats) and single cell necrosis of the tubular epithelium and cortical tubular atrophy (monkeys). Other kidney changes included proteinosis, hypertrophy of Bowman's capsule epithelium and an increased incidence of nephropathy (rats), atrophy of the cortical parenchyma, mixed cell infiltration in the papilla and hyperplasia of the papillary urothelium (dogs) and protein casts in the cortex, fibrosis of the interstitium and Bowman's capsule (monkeys). Renal toxicity was not associated with increases in blood urea nitrogen (BUN) or creatinine, except in one of six male monkeys given 75 mg/kg/day in the 12 month study. Urinalysis findings were generally negative, although increases in urinary protein and leukocytes were observed in the 6 month rat study.

Kidney histopathological changes were observed at clinically relevant exposures in all species examined: male rats at 25 mg/kg/day (ER 0.4) in the 6 month study, male dogs at 5 mg/kg/day (ER 0.9) in the 11 month study and mainly at the mid dose (MD) (25 mg/kg/day, ER 1.7) in the 12 month monkey study. The NOAEL in the monkey study was 5

mg/kg/day (ER 0.3), while no NOAEL was established in the pivotal rat or dog studies. Kidney histopathological changes were also found in some of the shorter duration studies. In rats, they were observed in one of the two 3 month studies and in the 14 week special study, with subtle changes (nuclear hypertrophy (cortex tubules)) observed after only 2 weeks in special study PD08-03. In dogs, an increased incidence of vacuolation of the tubular epithelium was observed in the 4 week study, but was not a finding in the 11 month study. In monkeys, necropsy/histology was not conducted in the 2 week study.

Some reversibility of DMF-induced histopathological changes was generally observed after treatment free periods in all three species, although this was less apparent after longer dosing durations, for example in the 6 month rat study, while in the 12 month monkey study in HD (75 mg/kg/day) males some changes (interstitial and Bowman's capsule fibrosis and cortical tubular atrophy) were observed at the end of the recovery period that were not seen at the end of treatment. Ki-67 immunohistochemical labelling, indicative of cellular proliferation, was clearly reduced after a treatment free period in the three special studies.

A consistent finding in the rat studies was a higher incidence of most changes in males than in females, including chronic progressive nephropathy (CPN; a rodent-specific, age-related renal disease, particularly of male rats) which was increased in incidence in the 6 month study, the 14 week special study and the rat carcinogenicity study. CPN confounds the interpretation of toxicity studies as it is difficult to distinguish which changes are directly drug-induced and those which are due to an exacerbation of CPN. However, some changes such as hypertrophy of tubular and Bowman's capsule epithelia observed in the 6 month rat study are not normally associated with CPN.

Since renal toxicity was observed in the laboratory animal species at exposures similar to those expected at the MRHD, special studies were conducted in the rat to search for possible non invasive biomarkers for early DMF-induced renal histopathology that could be incorporated into Phase III clinical trials to reveal any nephrotoxic effects in patients. The biomarkers examined were the non-specific renal injury marker, kidney injury molecule 1 (KIM-1) (a transmembrane protein that is expressed at low levels in normal kidney but is upregulated in proximal tubular cells after ischaemic or toxic injury), and albumin, β_2 microglobulin, and the lysozomal enzyme, N-acetyl-β-D-glucosaminidase (NAG), all markers of tubular injury, with urinary albumin providing an assessment of both glomerular filtration and proximal tubular resorption capabilities.

In the first study (PD08-03), a short duration of treatment (14 day treatment) was chosen to separate the effects of DMF treatment from CPN. However, the changes induced by oral DMF at 250 mg/kg/day over the 14 day period were relatively mild, with histopathological changes being limited to nuclear hypertrophy (cortical tubules), and increases in mean Ki-67 positive nuclei being non significant. Urinary biomarkers were either not affected (albumin and β_2 microglobulin), or transiently affected (increase on day 1 only, possibly due to decreased urine volume on this day; no effects on days 8 or 14 (KIM-1 and NAG)). The minimal effect on urinary biomarkers correlated with the minimal effects on the kidney.

In the second study (P00012-08-01), 250 mg/kg/day PO was the HD, but a 14 week duration was chosen. This dose and duration were known to elicit renal injury in rats, at least in males (male fertility study). The study established a correlation between urinary albumin and DMF-induced renal histopathological changes in rats, suggesting that urinary albumin may be suitable as a biomarker for DMF-induced renal toxicity in this species. However, the extent to which the urinary albumin simply reflected DMF-induced exacerbation of CPN is unknown, a problem which may have been reduced by selection of a strain less susceptible to this effect. Significant increases in urinary albumin in males were not observed until Day 56, reflecting the time for sufficient renal injury to occur to induce the increase in this biomarker. It is not clear why increases in KIM-1 were observed

in females but not in males in this study. Some of the changes induced by DMF were proliferative (as revealed by the Ki-67 data) and these might not be expected to be detected via a marker based on tubular function.

The validity of albumin as a biomarker of renal toxicity has been confirmed recently by the Predictive Safety Testing Consortium (PSTC) Nephrotoxicity Working Group to the FDA and European Medicines Agency (EMA).[12] The group qualified urinary albumin as a biomarker for drug-induced acute kidney alterations in rat studies and as a clinical bridging biomarker appropriate for use in clinical trials for monitoring kidney safety when animal toxicology findings generate a concern for tubular injury or glomerular alterations. The work by Yu *et* al. (2010)[13] is also supportive of the value of urinary albumin as a biomarker for the early detection of acute renal tubular injury in humans. Based on the findings from the rat studies, monitoring (every 3 months) for the renal markers, albumin and β2-microglobulin, was included in Phase III MS studies. While these studies will be evaluated by the clinical evaluator, in the sponsor's Summary of Clinical Safety it was noted that '*BG00012 was not associated with an increased risk of renal or urinary events. While small increases in the incidence of AEs of proteinuria and/or microalbuminuria were observed with BG00012 treatment, for the BG00012 BID dose the AE data were not corroborated by laboratory analyses…*'. It is noted that proteinuria and rate reports of renal tubular toxicity leading to renal tubular acidosis have been reported with Fumaderm.

Genotoxicity

An acceptable set of GLP compliant genotoxicity studies was submitted for both DMF and MMF. For DMF, studies included a bacterial reverse mutation test, a forward mutation test (HGPRT locus in CHO V79 cells), two *in vitro* chromosome aberration studies in cultured human lymphocytes and an *in vivo* rat micronucleus test. For MMF, studies included a bacterial reverse mutation test, an *in vitro* chromosome aberration study in cultured human lymphocytes and an *in vivo* rat bone marrow cytogenetic test, the latter conducted on MMF calcium salt. Generally, all studies were well conducted, with appropriate doses/concentrations. Some of the studies on DMF dated back to 1989 and standards have improved subsequently but the 1989 chromosome aberration test on DMF was repeated in 2006 to more modern standards (for example, statistical analysis conducted on the number/percentage of cells with aberrations rather than the number of aberrations; treatment in the absence of metabolic activation for 3 h as well as 22/24 h, achievement of acceptance criteria for a valid test). The bacterial reverse mutation test on DMF was one of the 1989 studies and did not include a strain (such as TA 102 or *E. coli* WP2*uvra*) that detects point mutations at A-T sites. The rat bone marrow cytogenic test with MMF calcium salt tested only one dose level. The use of males only in the rat micronucleus test (DMF) is acceptable, given the generally similar pattern of toxicity observed in male and female rats in the toxicity studies, and the similar metabolic, excretion and tissue distribution patterns in the two genders, even though MMF exposures tended to be slightly higher in females than males. However, this study did not include an initial range finding test, and the HD (1000 mg/kg PO) is considered suboptimal; it did not induce any clinical signs and was below the dose that induced clinical signs in the acute oral toxicity study in the rat (2610 mg/kg). The justification for this dose was based on an LD_{50} value of 1400 mg/kg PO. The source of this value was not stated and the value is lower than the values from the submitted acute oral rat toxicity study (3220 and 2630 mg/kg in males and females, respectively).

[12]Dieterle *et al*. (2010) Renal biomarker qualification submission: a dialog between the FDA-EMEA and predictive safety testing consortium. Nature Biotechnology 28, 455-462.
[13]Yu, Y., Jin, H., Holder, D., Ozer, J.S., Villarreal, S., Shughrue, P., Shi, S., Figueroa, D.J., Clouse, H, Su, M., Muniappa, N., Troth, S.P., Bailey, W., Seng, J., Aslamkhan, A.G., Thudium, D., Sistare, F.D. and Gerhold, D.L. (2010) Urinary biomarkers trefoil factor 3 and albumin enable early detection of kidney tubular injury. Nature Biotechnology 28, 470-477.

The results of the genotoxicity studies were negative with the exception of the 3 chromosome aberration studies, which were positive but only in the absence of metabolic activation and not under all conditions (see Table 7 below).

Table 7. Genotoxicity

Study no.	Drug	Experiment (result)	Treatment time (h)	Concentra t-ion (µg/mL)	Number of aberrations*	Number/ % of cells with aberrations*	% Mitotic index reduction
5407/89	DMF	1 positive	24	0 6.25 12.5 25 Pos. control	1 8 **29** **99**# **21**	^	NA 33 71 67 50
		2 positive	24	0 6.25 12.5 25 Pos. control	0 2 **5**§ 11^ **26**	^	NA 0 69 77 38
PD00012-04-16	DMF	1 positive	3	0 29.7 42.4 60.5 Pos. control	NA	0.5 4.5 **22.4** **56.0** **34.0**	NA 1 41 56 ND
		2 negative	22	0 7.5 Pos. control	NA	0 2.5 **44.0**	NA 58 ND
PD00012-08-03	MMF	1 positive	3	0 312 446 Pos. control	NA	0.5 **6.0** **8.5** **37.3**	NA 39 56 ND
		3 positive	22	0 28.8	NA	0 3.0	NA 32

Study no.	Drug	Experiment (result)	Treatment time (h)	Concentration (µg/mL)	Number of aberrations*	Number/ % of cells with aberrations*	% Mitotic index reduction
				41.0 Pos. control		**4.0** **46.0**	54 ND

* excluding gaps; § only 69 metaphases scorable; ^ not analysed statistically (only 4 metaphases scorable); # 99% of metaphases were pulverised; NA = not applicable; ND = no data; values in bold are significant

The positive results in Study 5407/89 at 12.5 and 25 µg/mL were confounded by particularly high cytotoxicity, with reductions in mitotic index in the range 67-77%; also indicative of excessive toxicity was that 99% of metaphases were pulverised at 25 µg/mL in experiment 1, and that only 69 and 4 cells had metaphases of sufficient quality for evaluation in experiment 2 at 12.5 and 25 µg/mL, respectively (normally 100 metaphases are scored). Statistical significance giving the positive result for experiment 1 in study PD00012-08-03 was probably only achieved due to the zero number of cells with aberrations in the vehicle control. Thus, clearly positive results were only achieved with 3 h treatment with DMF in Study PD00012-04-16 and with 3 h treatment with MMF in Study PD00012-08-03. In both cases, the higher concentration giving significant results showed high cytotoxicity (56% reduction in mitotic index). The positive finding for DMF seems unlikely to be of biological relevance because DMF is completely metabolised presystemically after oral administration in humans. The enzymes present in the S9 mix that are responsible for the conversion of DMF to compounds negative in chromosomal aberration assays will be hepatic esterases which rapidly degrade DMF in liver S9 mix[10] and not those of the TCA cycle, as this cycle takes place in the mitochondria which are sedimented in the 9000g centrifugation used in preparing an S9 mix.

A weight of evidence approach considering all genotoxicity studies suggests a low risk of genotoxicity in the clinic, since studies were either negative or the findings of low relevance, except for positive chromosome aberrations in human lymphocytes with MMF after 3 h treatment in the absence of metabolic activation.

Carcinogenicity

Carcinogenicity studies (up to 104 weeks duration) using the oral (clinical) route were conducted in mice and rats, metabolically appropriate species for investigating the potential carcinogenicity of DMF, although exposure ratios that could be achieved in the rat were relatively low. Both studies were GLP-compliant, well conducted, had appropriate animal numbers (75/group in both species) and included 4 dose levels, as well as a control group.

Dose levels were selected based on the results of the repeat dose toxicity studies. While a dose of 400 mg/kg/day in the 3 month mouse study was without effect on body weight gains, the initial HD selected for the carcinogenicity study (600 mg/kg/day) proved too high. In rats, dose levels of 100 and 150 mg/kg/day in males, while adequately tolerated, resulted in reduced survival necessitating early cessation (Weeks 80 and 82) of dosing and early sacrifice (Weeks 86 and 88). The majority of treatment-related deaths were due to severe lesions observed in the heart, non glandular stomach and kidneys. Despite the early terminations of the 100 and 150 mg/kg/day groups in male rats and the 400 mg/kg/day

group in mice, the studies are considered adequate for revealing the carcinogenic potential of DMF.

In both mice and rats (both genders), DMF induced tumours in the non glandular stomach (squamous cell papilloma/carcinoma in both species, and leiomyosarcoma and fibrosarcoma in mice). It also induced relatively low incidences of kidney tumours in both species and both genders (renal tubular adenomas (mice and rats) and renal tubular carcinomas (male mice and female rats)).

In male rats, DMF also induced tumours in the parathyroid (adenoma; not significant), and an increased incidence of interstitial (Leydig) cell adenomas in the testes. A significant increase in granular cell tumours in the cerebrum in HD male rats (2/74, 2.7%), although outside the historical control range for the animal supplier (2.0%) seems unlikely to be treatment related because the HD male group was the only group in which such tumours were observed and there were no non-neoplastic findings in the brain of either gender at any dose level.

In the mouse carcinogenicity study, there was an increase in the incidence of retinal degeneration at 400 mg/kg/day in males and at 200 and 400 mg/kg/day in females. A similar finding was not seen in the rat carcinogenicity study or in any of the repeat dose toxicity studies. Ophthalmological examinations, when conducted, were negative in all the repeat dose studies. This finding is therefore not considered of concern.

Stomach

A number of tumours in the non glandular stomach were observed in the mouse carcinogenicity study in both genders (papilloma, squamous cell carcinoma, leiomyosarcoma and, additionally in females only, fibrosarcoma). Incidences of papilloma and squamous cell carcinoma were significant at the MD and/or HD (ER 4 and 12, respectively). Similarly, stomach tumours were observed in the rat carcinogenicity study in both genders (non glandular squamous cell papilloma and carcinoma). Incidences of both tumour types in males and of the papillomas in females were significant at all dose levels (ER ≥0.5).

These tumours induced by DMF in the non glandular stomach of both mice and rats are not considered of clinical relevance for the same reasons that the non-neoplastic findings in the non glandular stomach were not considered relevant (see '*Repeat Dose Toxicity*').

Kidney

In the mouse carcinogenicity study, renal tubular adenomas were observed in both genders (trend significant) and renal tubular carcinomas, in males (trend significant) (both are rare tumours). Incidences of renal carcinomas in males were significant (pairwise comparisons) at 200 and 400 mg/kg/day (4/75 and 3/75, respectively; ER 4 and 12, respectively), although the incidence was also raised at 75 mg/kg/day (2/75 versus 0 in the concurrent control group; ER 1.3). Incidences of renal adenomas in females were significant (pairwise comparisons) at 400 mg/kg/day. Historical control data were not available for carcinomas but observed incidences of adenomas (including the control group incidence in males (1/75, 1.3%)) lay outside historical control values from the testing facility and from the literature[14], although historical control values from the testing laboratory were limited (low animal numbers, ≤360). Incidences of renal tubular hyperplasia were increased in both genders at all dose levels (ER ≥0.4; broadly dose-related).

In the rat carcinogenicity study, renal tubular adenomas (rare tumour) were observed in males (significant trend) and renal tubular carcinomas (rare tumour) in females

[14]Baldrick, P. and Reeve, R. (2007) Carcinogenicity evaluation: comparison of tumor data from dual control groups in the CD-1 mouse. Toxicologic Pathology 35, 562-569.

(significant trend and significant at 150 mg/kg/day (ER 4) but the incidence was also raised at 100 mg/kg/day (2/75 versus 0 in the concurrent control group; ER 2). Historical control data from the testing facility were limited (low animal numbers (≤180)) and no data were available for renal tubule adenomas or carcinomas. Observed incidences of adenomas at 150 mg/kg/day (ER 4) in both sexes lay outside historical control values from the literature.[15] Incidences of carcinomas in females at 100 and 150 mg/kg/day also lay outside historical control values from the literature. Incidences of renal tubular hyperplasia, although not high, were observed at all dose levels in males (ER ≥0.5) and at ≥50 mg/kg/day in females (ER ≥1.1), and were broadly dose-related.

As discussed above (see '*Repeat Dose Toxicity*'), age-related CPN, a common pathological finding in rodents, was exacerbated by treatment with DMF in rats, particularly in males, and to a lesser extent in mice. In mice, CPN was not evident in the 3 month study but incidence appeared to be increased by treatment in males in the carcinogenicity study. The data were difficult to interpret due to the high incidence in the control groups (90.7-92.0%), the early termination of the HD group (400 mg/kg/day; both sexes) and a slight reduction in survival at 200 mg/kg/day (both sexes). A trend was observed over the dose range 25-200 mg/kg/day in males but there was no clear evidence of an increased incidence in females. Incidences reached a maximum of 96% (both sexes). Severity data (see Table 8 below) also showed a clear trend for an increase in males, although there was little evidence for an increase in females.

In rats, there was a dose related increase in the incidence of CPN in females; in males, control incidence was high (90.7%) and incidence was 100% in all treated male groups. Severity was increased in a dose related manner in both genders, with severity, like incidence, being higher in males than in females. CPN was a contributor to treatment-related deaths in both mice and rats. In summary, DMF exacerbated age related CPN in rats (particularly males), and in male mice but there was little evidence of exacerbation in female mice.

Table 8. Histopathological findings

a) Results for mice

DMF dose (mg/kg/day)	Males					Females				
	0	**25**	**75**	**200**	**600/400**	**0**	**25**	**75**	**200**	**600/400**
MMF exposure ratio*	-	0.4	1.3	4	12	-	0.4	1.3	4	12
Renal tubular adenoma (rare)	1	2	0	5	3	0	0	0	2	**4**
Renal tubular carcinoma (rare)	0	0	2	**4**	**3**	0	0	0	0	0
Renal tubular adenoma/carcinoma (rare)	1	2	2	**8**	**5**	0	0	0	2	**4**
Hyperplasia, tubular	1	7	16	40	15	-	7	8	13	13

[15]Giknis, M.L.A. and Clifford, C.B. (2004) Compilation of spontaneous neoplastic lesions and survival in Crl:CD®(SD) rats from control groups. Charles River Laboratories.

DMF dose (mg/kg/day)		Males					Females				
Nephropathy (incidence, n=75)		68	69	72	72	58	69	70	72	69	66
Severity of nephropathy (% of animals with nephropathy)	Minimal	26.5	20.3	11.1	4.2	3.4	18.8	48.6	19.4	30.4	19.7
	Mild	30.9	43.5	48.6	16.7	32.8	59.4	35.7	62.5	49.3	43.9
	Moderate	39.7	33.3	36.1	62.5	46.6	17.4	11.4	15.3	17.4	33.3
	Marked	2.9	2.9	4.2	16.7	17.2	4.3	4.3	2.8	2.9	3.0

* data for males and females combined; values in bold are significant

b) Results for rats

DMF dose (mg/kg/day)	Males					Females				
	0	**25**	**50**	**100**	**150**	**0**	**25**	**50**	**100**	**150**
MMF exposure ratio*	**-**	0.5	1.1	2	4	**-**	0.5	1.1	2	4
Renal tubular adenoma (rare)	0	0	1	1	4	1	0	0	0	2
Renal tubular carcinoma (rare)	0	0	0	0	0	0	0	0	2	**4**
Hyperplasia, tubular	-	5	5	15	11	-	-	4	4	9
Nephropathy (incidence, n=75)	68	75	75	75	75	49	55	68	69	73
Severity of nephropathy (grade)	2.04	2.71	3.16	3.52	3.53	0.95	1.32	1.84	2.44	3.24

* data for males and females combined; value in bold is significant

There is evidence in the published literature that CPN is associated with proliferation of epithelial cells of affected tubules[16,17] in an evaluation of 2 year carcinogenicity studies archived by the National Toxicology Program (NTP), found a significant increase in CPN severity in rats with renal tubule tumours compared with age-matched controls without renal tumours, suggesting a positive correlation between CPN and the development of

[16]Hard, G.C. and Kahn, K.N. (2004) A contemporary overview of chronic progressive nephropathy in the laboratory rat, and its significance for human risk assessment. Toxicol. Pathol. 32, 171-180.
[17]Seely, J.C., Haseman, J.K., Nyska, A., Wolf, D.C., Everitt, J.I. and Hailey, J.R. (2002) The effect of chronic progressive nephropathy on the incidence of renal tubule cell neoplasms in control male F344 rats. Toxicol. Pathol. 30, 681-686.

renal tubule tumours. Also, for a number of chemicals (hydroquinone[18], ethylbenzene[19] and quercetin[20]), there was a significant association linking the incidence of renal tubular tumours in rats to advanced (particularly end-stage) CPN. The tumours were mostly incipient or small, low-grade adenomas that occurred in rats with severe or end-stage CPN. Hard (1998)[21] proposed that a marginal increase in renal tubule tumours associated with chemicals that exacerbated CPN to advanced stages of severity represented a distinct and separate mechanism/mode of action for renal carcinogenesis. While the hypothesis of a CPN-associated mechanism of renal carcinogenesis would be difficult to prove unequivocally, there is substantial evidence to support it.

Hard *et al*. (2009)[22] argued that this increase in renal tubule tumours involving the exacerbation of CPN by a test chemical is a mode of action that is not relevant for species extrapolation to humans. This argument was based on a comparison of the biology and pathology of rat CPN with nephropathies found in humans in which they concluded that there appears to be no exact counterpart of rat CPN in humans.

When a compound exacerbates CPN and induces renal tumours, it is difficult to determine whether the renal carcinogenesis induced is caused by exacerbation of CPN or by another mechanism. Seely and Hard (2008)[23] and Hard *et al*. (2009) each suggested a set of criteria for determining whether the CPN mechanism is involved as a cause of rat renal tumourigenesis, and these are summarised below:

1. slight, but usually statistically significant, increase in renal tubule tumours usually only in rats (see below),
2. exacerbation of CPN to advanced degrees of severity at doses associated with tumour increase,
3. tumours are usually adenomas (typically basophilic) which are often of small size and borderline with atypical tubule hyperplasia,
4. absence of any cellular alterations indicative of direct chemical toxicity (that is, other modes of action for rat renal carcinogenesis do not occur (except a2μ-g nephropathy)), and
5. the chemical and its metabolites are not DNA reactive.

Regarding criterion (i), mice also develop a form of CPN that bears some resemblance to rat CPN[24], so there is at least a potential for the same mechanism to apply to this species. However, it appears that chemical exacerbation of spontaneous nephropathy is not as frequently encountered in mice as in rats, with apparently only one reported example

[18]Hard, G.C., Whysner, J., English, J.C., Zang, E. and Williams, G.M. (1997) Relationship of hydroquinone-associated rat renal tumors with spontaneous chronic progressive nephropathy. Toxicologic Pathology 25, 132-143.
[19]Hard, G.C. (2002) Significance of the renal effects of ethyl benzene in rodents for assessing human carcinogenic risk. Toxicological Sciences 69, 30-41.
[20]Hard, G.C., Seely, J.C., Betz, L.J. and Hayashi, S. (2007) Re-evaluation of the kidney tumors and renal histopathology occurring in a 2-year rat carcinogenicity bioassay of quercetin. Food and Chemical Toxicol. 45, 600-608.
[21]Hard, G.C. (1998) Mechanisms of chemically induced renal carcinogenesis in the laboratory rodent. Toxicol. Pathol. 26, 104-112.
[22]Hard, G.C., Johnson, K. and Cohen, S.M. (2009) A comparison of rat chronic progressive nephropathy with human renal disease – implications for human risk assessment. Critical Reviews in Toxicology 39, 332-346.
[23]Seely, J.C. and Hard, G.C. (2008) Chronic progressive nephropathy (CPN) in the rat: review of pathology and relationship to renal tumorigenesis. J Toxicol. Pathol. 21, 199-205.
[24]Wolf, D.C. and Hard, G.C. (1996) Pathology of the kidneys. In: Pathology of the Ageing Mouse. Volume 1. (eds. Mohr, U., Dungsworth, D.L., Capen C.C., Carlton, J.P., Sunberg, P.P. and Ward, J.M.) ILSI Press, Washington DC, pp. 331-344.

(quinapril[25]). In NTP carcinogenicity studies, in most cases of increases in renal tubule tumours in rats where the exacerbation of CPN mechanism may have applied, neither nephropathy exacerbation nor an increase in the incidence of renal tubule tumours was reported in the companion mouse studies.[26]

DMF meets criterion (v), but does not strictly meet criteria (i), (ii), (iii) or (iv). Regarding criterion (i), tumours not only occurred in rats, but also in mice, which is unusual. In fact, tumour incidences were higher in mice than in rats, even when the achievement of higher exposures in mice than in rats is taken into consideration.

Although the above criteria do not refer to differences between males and females, the literature data reveal a more pronounced effect in male rats than in females in most studies, consistent with more pronounced CPN in males than females. However, this was not the case for DMF in rats, and particularly notable were the findings of more carcinomas than adenomas in female rats, with carcinomas generally considered a more advanced form of tumourigenesis than adenomas.

With respect to criterion (ii), while in rats, nephropathy was exacerbated to an advanced degree, this did not appear to be the case in mice. The percentage of mice with marked nephropathy was low in all dose groups, being <5% with the exception of male mice given 200 and 600/400 mg/kg/day.

With respect to criterion (iii), neither in mice nor rats were tumours largely adenomas, with similar incidences of male mice with carcinomas as with adenomas, and with higher incidences of carcinomas than adenomas in female rats.

With respect to criterion (iv), DMF has direct nephrotoxic effects not related to CPN. Thus, some of the renal histopathological findings in mice and rats did not appear to be typical of CPN (see '*Repeat dose toxicity*', above) and there were findings in dogs and monkeys that do not suffer from CPN.

Although a CPN related mechanism may have made a contribution to the development of these tumours, since DMF does not largely meet the above criteria, it is not appropriate to disregard the renal tumour findings in mice and rats as irrelevant to humans because of a CPN related mechanism. These tumours may pose a risk to patients.

Looking broadly at the role of Nrf2 in cancer, given that this transcription factor up regulates genes coding for endogenous antioxidants, Phase II detoxifying enzymes and transporters, it might be expected that expression of Nrf2-dependent proteins will ameliorate or eliminate toxicants and carcinogens.8 However, upregulation of the Nrf2 pathway has been implicated in promoting the survival of cancer cells and it may be preferable to inhibit the Nrf2 pathway during chemotherapy.8

Testes

A dose-related increase in interstitial (Leydig) cell adenomas (rare tumours) was observed in male rats, with increases being significant at 100 and 150 mg/kg/day (ER 2 and 4, respectively). There was also a dose-related increase in the incidence of interstitial cell hyperplasia (as well as in incidences of testicular atrophy and germinal epithelium degeneration) in the rat carcinogenicity study. Increased incidences of interstitial cell hyperplasia were observed in the male rat fertility study (at 250 and 375 mg/kg/day) but were not observed in the repeat dose studies (at doses up to 200 mg/kg/day in the 6 month study or 250 mg/kg/day in the 3 month studies) in rats.

[25]Gough, A.W., Reundell, J.F., McGuire, E.J. and de la Iglesia, F.A. (1993) Histopathological findings in rodents reated two years with the angiotensin converting enzyme inhibitor, quinapril hydrochloride (abstract). Toxicol. Pathol. 21, 594.
[26]Lock, E.A. and Hard, G.C. (2004) Chemically-induced renal tubule tumors in the laboratory rat and mouse: Review of the NCI/NTP database and categorization of renal carcinogens based on mechanistic information. Crit. Rev. Toxicol. 34, 211-299.

Interstitial cell adenomas were not found in the mouse carcinogenicity study and increased incidences of interstitial cell hyperplasia were not observed in mice, dogs or monkeys in the repeat dose toxicity studies. It is well documented in the literature that rats are highly prone to interstitial cell adenomas following the chronic administration of compounds that alter androgen pathways.[27,28, 29] Thus, the increased incidence of interstitial cell adenomas observed in the rat carcinogenicity study is considered to be rat specific and of little relevance to humans.

Parathyroid

Parathyroid adenomas (rare tumours) were observed in male rats, mainly at 150 mg/kg/day, although the incidence was not significant (trend or pairwise). There was also a dose-related increase in the incidence of parathyroid hyperplasia in both genders, although incidences were higher in males. The development of these tumours is likely to be secondary to progressive nephropathy/renal failure, when the kidneys have a reduced ability to excrete phosphorus and to convert vitamin D to its active form. A consequence is the formation of insoluble calcium phosphate in the body, which results in hypocalcaemia, followed by increased secretion of parathyroid hormone, and hence, secondary hyperparathyroidism. Consistent with this proposed mechanism of tumour induction was the fact that CPN is particularly prevalent in male rats and that the parathyroid adenomas were observed only in male rats and the fact that increases in serum phosphorus were observed in some of the repeat dose toxicity studies in the rat but not in other species. Given the proposed mechanism for induction of these tumours, the human risk associated with these tumours is considered to be low.

Reproductive toxicity

A full set of reproductive toxicity studies (fertility and early embryonic development studies in male and female rats, embryofetal development studies in rats and rabbits and a pre/postnatal development study in rats) was submitted. Full toxicokinetic data (plasma MMF concentrations) were collected to support both embryofetal development studies, while single time point values were provided to reveal exposure in the female fertility and the pre/postnatal development studies. The male fertility study was not supported by toxicokinetic data but exposure can be estimated by extrapolation from data from the repeat dose toxicity studies (doses used in the fertility studies were not always identical to, but lay within the range of values available from the repeat dose studies). Studies were well conducted with appropriate designs (including adequate group sizes, timing and duration of treatment and measured parameters). No dose range finding studies were conducted for either the rat or rabbit embryofetal development studies, with doses based on available data from studies with Fumaderm. Dose selection for the pre/postnatal study was based on data from the rat embryofetal development study. The selected doses for all the reproductive toxicity studies were appropriate. The rabbit, as well as the rat, are appropriate models for humans, given that esterases and TCA cycle enzymes are common for all mammals.

[27]Prentice, D.E. and Meikle, A.W. (1995) A review of drug-induced Leydig cell hyperplasia and neoplasia in the rat and some comparisons with man. Human & Exp. Toxicol. 14, 562-572.
[28]Clegg, E.D., Cok, J.C., Chapin, R.E., Foster, P.M.D. and Daston, G.P. (1997) Leydig cell hyperplasia and adenoma formation: mechanisms and relevance to humans. Reprod. Toxicol. 11, 107-121.
[29]Cook, J.C., Klinefelter, G.R., Hardisty, J.F., Sharpe, R.M. and Foster, P.M.D. (1999) Rodent Leydig cell tumorigenesis: a review of the physiology, pathology, mechanisms, and relevance to humans. Crit. Rev. in Toxicol. 29, 169-261.

Relative exposure

Table 9. Relative animal: human exposure ratios

Species	Study	DMF dose (mg/kg/day)	MMF AUC_{0-t} (µg·h/mL)*	Exposure ratio#
Rat (SD)	Embryofetal development	25	4.51	0.5
		100	29.29	4
		250	77.49	9
Rabbit (NZW)	Embryofetal development	25	12.41	1.5
		75	56.49	7
		150	116.25	14
Human (MS patients)	Study 109MS101	240 mg BID^	8.205	–

* mean of values for GD7 and GD17 (rat)/G19 (rabbit); # = animal:human plasma AUC_{0-t}; ^480 mg/day = 9.6 mg/kg/day (317 mg/m^2/day) in 50 kg individual, 6.9 mg/kg/day (254 mg/m^2/day) in 70 kg individual.

Exposure ratios achieved in the reproductive toxicity studies were adequate. Placental transfer of MMF was demonstrated in both rats and rabbits in the embryofetal development studies, with samples taken from mothers at 0.5 h post dose on gestational day (GD) 17 or GD19, respectively (fetuses GD18 and GD20, respectively). Mean values (all dose levels) for fetal:maternal plasma ratios were 0.56 and 0.13 in rats and rabbits, respectively. No data were submitted for excretion of MMF in milk.

In the male fertility study at oral doses of DMF of up to 375 mg/kg/day, there were no effects on reproductive parameters (in particular, mating, pregnancies and litter parameters of the mated females) or on sperm (numbers and motility). Interstitial cell hyperplasia was observed in the testes at 250 and 375 mg/kg/day at incidences of 9/25 (36%; both dose levels), and as discussed above, with longer duration of treatment, this hyperplasia progressed to interstitial cell adenoma. Extrapolation of toxicokinetic data (at 250 mg/kg) from the two 3 month repeat dose rat toxicity studies suggested an exposure ratio of ~6 at 375 mg/kg/day (7-9 based on mg/m^2), which was the NOAEL for fertility and early embryonic development in the male rat.

In female rats, treatment with DMF at oral doses up to 250 mg/kg/day did not affect mating, pregnancies or litter parameters. Oestrus cycling was affected at 250 mg/kg/day (ER 5-6 based on mg/m^2; ER 4, based on data for non-pregnant rats from the two 3 month repeat dose toxicity studies), with oestrus stages/14 days being significantly reduced and rats with 6 or more consecutive days of dioestrus being significantly decreased. As the effects on oestrus cycling had no effect on fertility or litter parameters, the NOAEL for fertility and early embryonic development in female rats was 250 mg/kg/day.

In the embryofetal development study in rats, there was no evidence of a teratogenic effect of DMF when given at oral doses up to 250 mg/kg/day (ER 9). Litter parameters were also not affected by treatment, except for a reduction in fetal weight at the HD. This was associated with decreased food intake and a reduction in body weight gain over GD7-18, and a body weight loss over GD7-10, in HD dams. Numbers of ossification sites were

reduced in hindlimb metatarsals and phalanges in HD fetuses. A delay in ossification is a common finding associated with reduced fetal weights in rats. Given the reduced fetal weights and reductions in ossification sites at 250 mg/kg/day, the NOAEL for embryofetal development was 100 mg/kg/day (ER 4).

In the embryofetal development study in rabbits, there was no evidence of a teratogenic effect of DMF when given at oral doses up to 150 mg/kg/day (ER 14). Litter parameters were also not affected by treatment, however, 4/20 (20%) of HD does aborted over GD19-25. Abortions were associated with decreased food intake, and body weight loss in HD does over GD7-16. Given the lack of any embryofetal findings in this study, the NOAEL for embryofetal development was the HD (150 mg/kg/day, ER 14).

In the pre/postnatal development study in rats, with dose levels the same as those for the embryofetal development study, there were small but significant increases in length of gestation in all DMF-treated groups. This was possibly associated with treatment, although values were reported to lie within the historical control range for the testing facility (no data provided). Consistent with the results of the embryofetal development study, litter weights on Day 1 were reduced at the HD (250 mg/kg/day; ER 9). Again, this was associated with a reduction in body weight gain over GD7-20, and a body weight loss over GD7-10, in the HD dams. Litter weights remained reduced at the HD at the end of lactation (postnatal day (PND) 21), and in HD F_1 males[30] body weight gain over the postlactation period was reduced, and terminal body weights remained reduced. A delay in preputial separation was observed in HD F_1 males, presumably due to the reduction body weight in this group. There was no effect of treatment on survival of the F_1 generation at any stage of their development. In the Watermaze test, the increases in latency trials (both sessions) in HD F_1 males possibly reflected a reduction in maturity, given the continued reduction in body weights of this group throughout the study compared to controls. The changes in trials to criterion (Session 2) in the treated female groups were small and well within the historical control range (data provided). Thus, the reduction in Watermaze performance is unlikely to be of biological significance. Given the reduced pup weights at the HD, the NOAEL for pre/postnatal development in the rat was 100 mg/kg/day (ER 4).

Pregnancy classification

The sponsor has not proposed a Pregnancy Category. A category of B1[31] is recommended as studies in animals did not shown evidence of an increased occurrence of fetal damage.

Local tolerance

DMF appears to have irritant properties as revealed by its effects on the non glandular stomach in rodents. As the proposed formulation is an enteric-coated tablet within a gelatin capsule, the major site in the body that DMF will come into contact with after oral administration is the intestines (most likely small intestine). As discussed above, the proposed enteric-coated formulation was tested in the pivotal study (as well as the dose escalation study) in dogs. No toxic effects were observed in the intestines in the pivotal study at doses up to 50 mg/kg/day (ER 7), nor were any toxic effects observed in the oesophagus or stomach in this study. However, a more valid assessment of local tolerance may be obtained by comparing the actual (mg) dose administered. The 18 day escalation study used individual doses of up to 100 mg/kg (approximately 1000 mg) and the 11 month study used doses up to 37.5/25 mg/kg twice a day (BID) (approximately 375/250

[30]The F1 generation is the generation resulting immediately from a cross of the first set of parents (parental generation).

31Category B1: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.
Studies in animals have not shown evidence of an increased occurrence of fetal damage.

mg BID). Gastrointestinal (GI) signs featured prominently in both dog studies and, although the GI local area of exposure will differ between dogs and humans, these findings are consistent with the adverse GI effects reported in clinical trials at 240 mg BID (draft PI document). The NOAEL for GI effects in dogs (12.5 mg/kg dose BID, *ca* 125 mg BID) is similar to the temporary clinical dose reduction recommended to reduce GI side effects (draft PI document).

Ocular and skin irritation studies were not conducted because the product is an enteric-coated formulation and would not result in irritancy at these sites.

Fumaderm, containing DMF and monoethyl fumarate salts, was shown to have extremely sensitising properties in the Magnusson & Kligman skin sensitisation test in guinea pig. Although this property is probably a reflection of the activity of both DMF and monoethyl fumarate, it is unlikely to be of relevance in the clinical use of Tecfidera. There is a requirement to assess the sensitising potential only for products applied to skin, rectum or vagina.

Impurities

There are two organic impurities in the drug substance, MMF and FA, and both are metabolites in humans and the laboratory animal species.

Paediatric use

DMF is not proposed for paediatric use and no specific studies in juvenile animals were submitted.

Other studies

Studies on dependence were not required as DMF did not show any CNS activities that would be indicative of abuse liability.

Phototoxicity studies were not required as DMF and MMF do not absorb in the ultraviolet (UV)/visible light range 290-700 nm (DMF exhibits a single UV absorbance maximum at 209.9 nm).

No specialised immunotoxicity studies were required because results of the standard toxicity and carcinogenicity studies did not reveal a specific effect on the immune system (such as haematological findings, organ weights and histology of immune system organs, serum globulins, infections or tumours suggestive of immunosuppression).

Nonclinical summary

- An adequate dossier of nonclinical studies was submitted. Relevant studies were GLP compliant, with the exception of the cardiovascular safety study in dogs.
- DMF activates nuclear factor (erythroid-derived-2)-like 2 (Nrf2), a transcriptional factor that regulates antioxidant response. DMF was shown, both *in vitro* and *in vivo,* to have anti-inflammatory activity and neuroprotective activity. The concentrations and doses showing activity in the primary pharmacology studies were similar to, or slightly higher than, those which are clinically relevant.
- No secondary pharmacology studies were submitted. The mechanism for the flushing side effect was investigated in clinical studies. Safety pharmacology studies investigating potential CNS effects were of poor quality but there was little evidence of CNS effects from the range of studies submitted. Cardiovascular safety pharmacology studies included *in vitro* investigations of effects on cloned hERG currents, and on

action potentials in canine Purkinje fibres, and an *in vivo* cardiovascular and respiratory study in dogs. No effects of DMF or monomethyl fumarate (MMF; main metabolite) were observed in the *in vitro* studies at concentrations well above expected clinical levels. In the *in vivo* study up to doses well in excess of the clinical dose, there were no effects of DMF on ECGs or respiration and only quantitatively small effects on heart rate and blood pressure. Similarly, no consistent effects on ECGs were observed in the repeat dose toxicity studies.

- Orally administered DMF was rapidly (all species) and extensively (close to 100% in rats) absorbed. Plasma protein binding was low in all species but particularly in rats (0%) and monkeys (3%) and was highest in humans (23-40%). After oral administration of ^{14}C-DMF to rats, radioactivity was widely distributed to tissues. There was no evidence of melanin binding.
- DMF was extensively metabolised presystemically, with circulating parent drug not being detectible (humans, rats, dogs). MMF was rapidly and extensively metabolised in rats and humans, with a sizeable proportion of the dose being excreted as $^{14}CO_2$ within a short period of time in rats and humans. Glucose, and also fumaric acid + citric acid, were the main circulating metabolites in rats and humans. The proposed metabolic pathway was the same for all species and involves metabolism by esterases and TCA cycle enzymes, with no involvement of CYP enzymes. In both rats and humans, in addition to the major route of excretion via expired air, renal excretion was also substantial, while faecal excretion was minimal.
- There was no evidence of potential for pharmacokinetic drug interactions mediated by inhibition of CYP enzymes or P-glycoprotein or enzyme induction.
- Single dose toxicity studies were conducted in rats and mice, testing both the IP and PO routes in each species. LD_{50} values were high (about 1 g for both routes in mice and the IP route in rats, and about 3 g for the PO route in rats).
- Repeat dose toxicity studies (all using the oral route) were conducted in mice (up to 3 months), rats (up to 6 months), dogs (up to 11 months) and cynomolgus monkeys (up to 12 months). Major target organs identified were the non glandular stomach (forestomach) (mouse and rat), the kidney (rat, dog and monkey), testes (mouse and dog; also identified as a target organ in rats in the male fertility study) and the liver (rat).
- Findings in the non glandular stomach of rodents are considered of low risk to humans because there is no counterpart to the rodent non glandular stomach in humans and the proposed formulation is enteric coated microtablets within a gelatin capsule. The risk of testicular changes and liver toxicity in the clinic is also likely to be low (see discussions above).
- Increased kidney weights were observed in mice, rats, dogs and monkeys, while histopathological changes (generally minimal to mild), including tubular regeneration, were observed in the kidneys of the latter 3 species at clinically relevant exposures. Various other changes, mainly but not solely tubular, were individually observed in one or two, but not all 3, of these species. Urinary albumin was established as a marker for DMF-induced renal toxicity in the rat, although results were confounded by DMF-induced exacerbation of rodent-specific nephropathy. Urinary albumin and β_2 microglobulin were monitored in clinical trials, with apparently negative results. Clinical evaluation will indicate whether these data are sufficient to allay the concerns for renal toxicity revealed by the nonclinical data.
- A full dossier of genotoxicity studies was submitted for both DMF and MMF (bacterial reverse mutation studies, chromosome aberration studies in human lymphocytes, rat micronucleus (DMF) or rat bone marrow cytogenetic tests (MMF), plus a forward

mutation test at the HGPRT locus in CHO cells for DMF. Although there were some positive results in the chromosome aberration studies in the absence of metabolic activation, a weight of evidence approach suggests a low risk of genotoxicity in the clinic.

- Two year carcinogenicity studies were conducted in mice and rats. In both species, DMF induced tumours in the non glandular stomach which are considered of low risk to humans. It induced interstitial (Leydig) cell tumours in male rats but the rat is highly sensitive to these tumours and this finding is considered of low relevance to human risk. DMF also induced low incidences of kidney tumours in both species (renal tubular adenoma [mice and rats], and renal tubular carcinoma [male mice and female rats]). Incidences of at least one of these tumours were significantly increased at ER 4 in both species but some increases were observed at clinically relevant exposures. A mechanism of tumourigenesis related to exacerbation of rodent-specific nephropathy appears likely to make a contribution to, but not be solely responsible for, the development of these tumours. Thus, it is not considered appropriate to disregard these tumours as irrelevant to humans because of such a mechanism and they might pose a risk to patients.
- A full set of reproductive toxicity studies (fertility and early embryonic development studies in male and female rats, embryofetal development studies in rats and rabbits, and a pre/postnatal development study in rats) was submitted. Placental transfer of MMF was demonstrated in both rats and rabbits, but there were no data on excretion of MMF in milk.
- In the male fertility study, interstitial hyperplasia was induced in the testes, but there were no effects on reproductive parameters or on sperm. In the female fertility study, oestrus cycling was affected at 250 mg/kg/day PO (ER approximately 4) but this did not affect mating or pregnancies, and litter parameters were also not affected by treatment.
- In the rat embryofetal development study, there were no effects on embryofetal development, except for a reduction in fetal weight and numbers of ossification sites at the high (maternotoxic) dose. In the rabbit embryofetal development study, 20% of does aborted at the high (maternotoxic) dose, but there were no effects on the development of remaining fetuses. There was no evidence of teratogenicity in either species.
- The main finding in the pre/postnatal development study in rats was a reduction in litter weight (at birth and throughout lactation) at the high dose which was maternotoxic. Terminal body weights of high dose F_1 males remained reduced, and a delay in preputial separation and a reduction in performance in the Watermaze test in these males were probably associated with reduced maturity. Although it can never be ascertained definitively, the reproductive toxicity findings in the nonclinical studies seem likely to be due to maternal toxicity, and therefore their clinical relevance is considered to be low.

Conclusions and recommendation

- An adequate dossier of nonclinical studies was submitted.
- The primary pharmacology data support the use of DMF for the treatment of relapsing multiple sclerosis. However, the concentrations and doses showing activity in the primary pharmacology studies were similar to, or slightly higher than, those which are clinically relevant.

- The main target organs identified were the non glandular stomach (forestomach) (mouse and rat), the kidney (rat, dog and monkey), testes (mouse, rat and dog) and the liver (rat). The kidney findings were the only findings that are considered to be a risk in patients. Urinary albumin was established as a marker for DMF-induced renal toxicity in the rat, although results were confounded by DMF-induced exacerbation of rodent-specific nephropathy. Urinary albumin and β_2 microglobulin were monitored in clinical trials, with apparently negative results. Clinical evaluation will indicate whether these data are sufficient to allay the concerns for renal toxicity revealed by the nonclinical data.
- A weight of evidence approach suggests a low risk of genotoxicity in the clinic.
- Renal tubular adenomas and carcinomas were observed in the mouse and rat carcinogenicity studies. Incidences of at least one of these tumours were significantly increased at an animal/human exposure ratio of 4 in both species but some increases were observed at clinically relevant exposures. A mechanism of tumourigenesis related to exacerbation of rodent-specific nephropathy appears likely to make a contribution to, but not be solely responsible for, the development of these tumours. Thus, it is not considered appropriate to disregard these tumours as irrelevant to humans because of such a mechanism, and they might pose a risk to patients.
- Although it can never be ascertained definitively, the reproductive toxicity findings in the nonclinical studies seem likely to be due to maternal toxicity, and therefore their clinical relevance is considered to be low. The recommended pregnancy category is B1.
- Registration of DMF is supported provided that the clinical data are sufficient to allay concerns regarding renal toxicity, and that clinical efficacy is sufficient to outweigh concerns regarding renal carcinogenicity.
- Amendments to the draft Product Information were recommended but these are beyond the scope of this AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system (CNS) that predominantly affects young adults, causing plaques of demyelination. Plaques are most common in the white matter of the brain, spinal cord and optic nerves, but occasionally plaques affect the cerebral grey matter. The most common pattern of disease is that patients experience bouts of inflammation, or “relapses” in which plaques appear and cause symptoms, followed by periods of recovery, or “remissions”; this is known as relapsing and remitting MS. Eventually, due to a combination of incomplete recovery from attacks and some background progression of disease between attacks, patients develop a progressive form in which individual relapses are no longer a major feature; this is known as secondary progressive MS (SPMS). Some patients show progressive disease from the outset, without identifiable relapses, and this is known as primary progressive MS (PPMS).

The aetiology of MS is complex and not fully understood but most models propose an autoimmune process directed against myelin. Most available treatments for MS are either

directed at symptom management (anti-spasm treatment, pain relief, bladder relaxants) or at modifying the inflammatory cascade that leads to demyelination. Anti-inflammatory treatments include corticosteroids, which may ameliorate relapses, or immunomodulatory agents that may reduce the frequency of relapses and delay progression of disease.

For many years, the most widely used immunomodulatory agents in MS have been beta-interferons, which require subcutaneous or intramuscular injections one or more times per week, and glatiramer acetate, which requires daily subcutaneous injection. Both groups of agents may cause injection-site reactions and the beta interferons have been associated with flu-like symptoms, mood changes and fatigue. The chemotherapy agent mitoxantrone has also been used but this agent causes cumulative cardiotoxicity. Monthly infusions of natalizumab have been shown to be effective but come with a risk of causing progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the CNS. More recently, the oral agents cladribine and fingolimod have been approved for use in Australia but both have some safety concerns and cladribine is no longer marketed. Fingolimod, the most widely used of the new oral agents, has been associated with sudden death and may cause macular oedema. There is a clear need for additional oral agents to be developed as disease modifying drugs in MS.

The precise mechanism of action of DMF in MS is unclear but it appears to have anti-inflammatory and neuroprotective properties. According to the sponsor, its pharmacodynamic effects "appear to be predominately mediated through activation of the nuclear factor (erythroid-derived 2)-related factor 2 (Nrf2) antioxidant response pathway, which is the primary cellular defence system for responding to a variety of potentially toxic stimuli." It may also have an immunomodulatory or anti-inflammatory action. In a variety of animal models, including collagen-induced arthritis (CIA) and experimental autoimmune encephalitis (EAE), DMF was observed to reduce cytokine production and inflammation. EAE is an animal model of antigen-induced CNS inflammation that has many parallels with MS, and efficacy in this setting suggests that a similar benefit might be achieved in humans with MS.

Contents of the clinical dossier

Guidance

The sponsor designed the pivotal efficacy studies in accordance with recommendations from the US National MS Society's International Advisory Committee on Clinical Trials of New Agents in MS [Polman 2008] and TGA adopted European Union "Guideline on Clinical Investigation of Medicinal Products for the Treatment of Multiple Sclerosis" (CPMP/EWP/561/98 Rev. 1).[32]

The sponsor also sought guidance through from scientific-advice meetings in Europe and the US. The main issue addressed was the ethics of performing a placebo-controlled study in MS, when several active agents are known to be effective.

The main recommendations that were incorporated into the pivotal studies as a result of this guidance were (1) the inclusion of subjects who could not be controlled by established effective therapies; (2) subjects had to be aware of and decline locally approved MS therapies; (3) the consent forms stated that, by choosing to participate in a placebo-controlled study, the subject was potentially delaying treatment, which could negatively impact their disease course; (4) subjects had to be *re-consented* when they had experienced confirmed relapse or disability progression.

[32] <http://www.tga.gov.au/pdf/euguide/ewp056198en.pdf>

Scope of the clinical dossier

The submission contained the following clinical information:

- 10 clinical pharmacology studies, all of which provided pharmacokinetic data and 1 of which also provided pharmacodynamic data (a QT-prolongation study). A couple of additional PD studies were mentioned but not submitted for critical evaluation.
- 2 pivotal efficacy/safety studies.
- 1 dose-finding efficacy study.
- (sponsor's) Summary of Clinical Pharmacology, Summary of Clinical Efficacy, Summary of Clinical Safety.

Paediatric data

The submission did not include paediatric data. MS is relatively rare in the paediatric age group, and it is unlikely that an adequately powered study of DMF in paediatric subjects could ever be performed.

Good clinical practice

The sponsor provided a statement that all studies were conducted in accordance with the principles of Good Clinical Practice.

Pharmacokinetics

Studies providing pharmacokinetic data

Table 10 below, shows the studies relating to each pharmacokinetic topic and the location of each study summary.

Table 10. Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID	*
PK in healthy adults	General PK - Single dose	IKP/ID33	*
		109HV101	
		109HV102	*
	- Multi-dose	FG-PK-03/04	*
	Bioequivalence†	n/a	
	Food effect	FG-PK-02/02	*
		C-1903	*
PK in special populations	Target population § - Single dose	109MS101	*
	- Multi-dose	n/a	
	Hepatic impairment	n/a	

PK topic	Subtopic	Study ID	*
	Renal impairment	n/a	
	Neonates/infants/children/adolescents	n/a	
	Elderly	n/a	
Genetic/gender-related PK	Males versus females	n/a	
PK interactions	Aspirin (ASA)	109HV106	*
	Avonex (Interferon β-1a)	109HV103	*
	Copaxone (glatiramer acetate)	109HV104	*
Population PK analyses	Healthy subjects	n/a	
	Target population	n/a	
	Other	n/a	

* Indicates the primary aim of the study. † Bioequivalence of different formulations. § Subjects who would be eligible to receive the drug if approved for the proposed indication.

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

Evaluator's overall conclusions on pharmacokinetics

Overall, the PK of BG00012 has been adequately studied, though some features of the PK profile remain unexplained. Dimethyl fumarate (DMF) is rapidly and completely converted to the active agent momomethyl fumarate (MMF) before reaching the systemic circulation. Bioavailaibility is high, as indicated by the very low proportion (<1%) recoverable from the faeces.

BG00012 microtablets are protected by an enteric coating, so absorption does not commence until the microtablets leave the stomach. The time of peak concentration of MMF is variable but usually occurs in 2-2.5 h. MMF is distributed with an apparent volume of distribution of around 60-70 L. Following 240 mg administered twice a day with food, the median peak (C_{max}) in MS subjects was 1.72 mg/L and overall (AUC) exposure was 8.02 mg.h/L. Many individuals show multiple peaks in plasma concentration, for unknown reasons. Human plasma protein binding of MMF generally ranges between 27%-40%.

MMF is metabolised in the Krebs cycle in mitochondria and it is largely excreted as CO_2, with a terminal half-life of about one hour. Exhalation of CO_2 accounts for approximately 60% of a radioactive dose, whereas renal and faecal elimination account for 15.5% and 0.9% of the dose respectively.

Exposure to MMF (C_{max} and AUC) is dose proportional and there is no significant difference between single and multi-dose pharmacokinetics.

Body weight is the main covariate of exposure (C_{max} and AUC) in relapsing remitting multiple sclerosis (RRMS) subjects. Gender, age and race did not have a statistically

significant impact on C_{max} or AUC. (The PK of MMF did show statistically significant gender differences but these are almost entirely accounted for on the basis of weight.) There is very limited information about the PK of MMF in the elderly and no information relating to the paediatric setting.

The pharmacokinetic profile of MMF does not indicate a high likelihood of interactions with other drugs and there was no evidence of interactions with beta interferon, glatiramer acetate, aspirin or alcohol. The dose is not likely to need adjustment in the setting of moderate renal or hepatic impairment, given that renal elimination accounts for only 15.5% of an administered dose and hepatic enzyme systems are not involved in its metabolism, though the PK of MMF has not been directly studied in the setting of renal or hepatic impairment. PK in the MS population is not different to that in healthy volunteers.

Pharmacodynamics

Studies providing pharmacodynamic data

No primary pharmacodynamic (PD) studies were submitted and the mechanism of action of BG00012 remains unclear. The PD studies that were performed were largely limited to exploring tolerability (in particular, potential mediators of flushing), cardiac safety (QT interval) and some aspects of the effect of BG00012 on the Nrf2 pathway (which relates to one theory of a potential mechanism of action). Not all PD studies were submitted for critical evaluation: Study PK01/02 and Study 09RA201 were merely described in the sponsor's Summary of Clinical Pharmacology.

None of the pharmacodynamic studies had deficiencies that excluded their results from consideration but the studies contributed little to the understanding of how BG00012 exerts its effects.

Activation of the Nrf2 pathway was assessed in a sub-study of the pivotal Phase III Study, 109MS301; the design of this study is described in the *Efficacy* section but the PD sub-study is described under *Primary Pharmacodynamics* (see Attachment 2).

Evaluator's overall conclusions on pharmacodynamics

The precise mechanism of action of BG00012 in MS remains unclear but there is some evidence that it modifies activation of the NRf2 pathway which plays a role in defending cells from oxidative stress. It remains unclear whether other potential mechanisms, such as immune modulation, might play a more important role.

Efficacy

Dosage selection for the pivotal studies

In both of the pivotal studies (Studies 109MS301 and 109MS302), the sponsor assessed two dose regimens of BG00012: 240 mg twice daily (BID), which is the proposed dose and 240 mg three times daily (TID).

According to the sponsor, the 240 mg TID dose was selected on the basis of Study C-1900, a randomised, double-blind, placebo-controlled, dose-ranging study in which 257 subjects received either BG00012 (120 mg daily, 120 mg TID, or 240 mg TID) or placebo for 24 weeks. Subjects receiving BG00012, 240 mg TID, had significant reductions in brain lesions and annualised relapse rate compared with subjects who received placebo. The lower BG00012 dose regimens (120 mg TID and 120 mg daily) did not have a significant effect on any of the efficacy endpoints but note that BID dosing was not evaluated and the

middle dose group had a total daily dose (360 mg) less than the standard proposed dose. All 3 dose regimens in Study C-1900 were generally well tolerated.

Study C-1900 thus showed that 240 mg TID was effective and had acceptable tolerability, so it was chosen for the Phase III studies. An intermediate dose regimen, 240 mg BID, was also chosen for evaluation in the Phase III studies. This rationale seems reasonable and means that the Phase III studies assessed doses with a balance between efficacy and tolerability.

The sponsor's submission rests on two pivotal efficacy studies, Study 109MS301 and Study 109MS302 (hereafter, Study 301 and 302). Supportive efficacy data comes from a Phase II dose-ranging study, C-1900 and an extension study, Study 109MS303 (hereafter, Study 303).

Table 11. List of BG00012 efficacy studies

Study Number	Study Design	Treatment Regimens
C-1900	Phase 2, randomized, multicenter, placebo-controlled, double-blind, parallel-group, dose-ranging study	• Placebo (during Part 1) • BG00012 120 mg QD • BG00012 120 mg TID • BG00012 240 mg TID
109MS301	Pivotal Phase 3 randomized, multicenter, double-blind, rater-blind, placebo-controlled, dose-comparison study designed to determine the efficacy and safety	• Placebo • BG00012 240 mg BID\ • BG00012 240 mg TID
109MS302	Pivotal Phase 3 randomized, multicenter, double-blind, rater-blind, placebo-controlled, active reference comparator, dose-comparison study designed to determine the efficacy and safety	• Placebo • BG00012 240 mg BID • BG00012 240 mg TID • GA 20 mg QD SC
109MS303	Phase 3 multicenter, parallel-group, randomized, dose blind, rater-blind, dose-comparison extension study	• BG00012 240 mg BID • BG00012 240 mg TID

BID = twice daily; GA = glatiramer acetate; TID = 3 times daily; QD = once daily; SC = subcutaneous

Pivotal efficacy studies

The sponsor submitted two pivotal efficacy studies, which had very similar designs: both were randomised, double-blind, and placebo-controlled studies in which subjects with RRMS were treated for 2 years. Both were designed to have sufficient statistical power to detect a reduction in relapses, which was the primary efficacy focus in each study but relapses were analysed differently in the two studies. Study 301 assessed the *proportion of patients relapsed,* whereas Study 302 assessed *annualised relapse rate.* Both methods are acceptable but the annualised relapse rate is a more conventional efficacy endpoint, used in many other MS studies; it is potentially more sensitive than the proportion of subjects relapsed because it incorporates data about second and subsequent relapses in the same subject. On the other hand, the mean annualised relapse rate could be dominated by a small number of subjects with frequent relapses (who would only be counted once with a "proportion relapsed" approach).

Secondary endpoints in the two studies were similar, as shown in the table below.

Apart from using slightly different primary endpoints, another key difference between the pivotal studies was that Study 302 employed an active control, glatiramer acetate, as well as placebo.

Table 12. Efficacy endpoints in pivotal studies. Primary, secondary and selected tertiary efficacy endpoints in studies 301 and 302 and for the integrated analysis of pooled data.

Efficacy Endpoints *(measured at or over 2 years comparing BG00012 to placebo)*	**Study 301**	**Study 302**
Primary endpoint	Proportion of subjects relapsed	Annualized relapse rate
Secondary endpoints (listed in descending rank order)	Number of new or newly enlarging T2 hyperintense lesions	Number of new or newly enlarging T2 hyperintense lesions
	Number of Gd-enhancing lesions	Number of new T1 hypointense lesions
	Annualized relapse rate	Proportion of subjects relapsed
	Disability progression measured by EDSS	Disability progression measured by EDSS
Tertiary endpoints	Number of new T1 hypointense lesions	Number of Gd-enhancing lesions
	MSFC	MSFC
	EQ-5D and VAS	EQ-5D and VAS
	SF-36	SF-36
	Brain Atrophy	Brain Atrophy
	Whole Brain MTR	Whole Brain MTR

EDSS =Expanded Disability Status Scale (only protocol-defined progression sustained for at least 12 weeks); MSFC = Multiple Sclerosis Functional Composite; EQ-5D = European Quality of Life 5-Dimensions Health Survey; VAS = Visual Analogue Scale; SF-36 = Short Form-36 Health Survey; MTR = magnetization transfer ratio

Evaluator's conclusions on clinical efficacy

The important endpoints from both pivotal studies are tabulated below. Active treatment with BG00012 for "2 years" (96 weeks) at the proposed dose of 240 mg BID reduced the proportion of subjects relapsing from 0.461 to 0.270, in Study 301 (where this parameter was the primary endpoint) and from 0.410 to 0.291 in Study 302. Both reductions were statistically significant. This endpoint was reported in a potentially misleading manner in the sponsor's Summary of Clinical Efficacy and the proposed PI, and the sponsor should clarify the cumulative relative risk reduction for this endpoint prior to final approval of the PI.

Most pivotal MS studies for other agents have used the annualised relapse rate as their primary endpoint. Active treatment with BG00012 reduced the annualised relapse rate from 0.364 to 0.172, in Study 301 and from 0.401 to 0.224, in Study 302 (where this parameter was the primary endpoint). This corresponds to relative reductions of 53% and 44%, respectively. These reductions were highly statistically significant, and they were of a magnitude likely to be of clinical value. The reductions in relapse rate with BG00012 were broadly comparable to reductions seen with other disease-modifying treatments in MS, although direct comparisons across different studies are inappropriate

Treatment with BG00012 240 mg BID was also associated with highly significant reductions in disease activity as assessed by MRI, in both clinical studies, for a range of individual MRI parameters including the major MRI parameter, new or newly enlarging T2 lesions.

Results for disability progression were less consistent. In Study 301, BG00012 240 mg BID reduced the proportion of patients progressing from 0.271 to 0.164 and this was highly significant (p=0.005). In Study 302, the proportion progressing was reduced from 0.169 to 0.128, which was favourable but not significant (p=0.25). In a pooled analysis, the overall effect on disease progression was significant (32% risk reduction, 95%CI 12.1 to 47.6%).

Efficacy results for the 240 mg TID regimen were generally similar to the 240 mg BID regimen, which supports the validity of the results.

Table 13. Pivotal phase III studies 301 and 302 individual efficacy results at 2 years.

	Study 301				Study 302			
Endpoint	**Placebo**	**240 mg BID**	**240 mg TID**	**Endpoint**	**Placebo**	**240 mg BID**	**240 mg TID**	**GA**
Primary								
Proportion relapsing[1]	0.461	0.270 p<0.0001[a]	0.260 p<0.0001[a]	**Annualized relapse rate**	0.401	0.224 p<0.0001[b]	0.198 p<0.0001[b]	0.286 p=0.0128[b]
Secondary (listed in descending rank order)								
New or newly enlarging T2 hyperintense lesions (adjusted mean number)	17.0	2.6 p<0.0001[b]	4.4 p<0.0001[b]	**New or newly enlarging T2 hyperintense lesions** (adjusted mean number)	17.4	5.1 p<0.0001[b]	4.7 p<0.0001[b]	8.0 p<0.0001[b]
GdE lesions (mean number)	1.8 [2]	0.1 p<0.0001[c]	0.5 p<0.0001[c]	**New T1 hypointense lesions** (adjusted mean number)	7.0	3.0 p<0.0001[b]	2.4 p<0.0001[b]	4.1 p=0.0021[b]
Annualized relapse rate	0.364	0.172 p<0.0001[b]	0.189 p<0.0001[b]	**Proportion relapsing**[1]	0.410	0.291 p=0.0020[a]	0.241 p<0.0001[a]	0.321 p=0.0097[a]
Disability progression (proportion progressing[2])	0.271	0.164 p=0.0050[a]	0.177 p=0.0128[a]	**Disability progression** (proportion progressing[2])	0.169	0.128 p=0.2536[a]	0.130 p=0.2041[a]	0.156 p=0.7036[a]
Tertiary								
New T1 lesions (adjusted mean number)	5.6	1.5 p<0.0001[b]	2.1 p<0.0001[b]	**Gd+ lesions** mean number)	2.0	0.5 p<0.0001[c]	0.4 p=0.0001[c]	0.7 p=0.0003[c]

NOTE: All p-values compare each active treatment group versus placebo based on [a] Cox proportional hazards model, [b] negative binomial regression, [c] ordinal logistic regression

[1] From Kaplan-Meier curve of time to relapse
[2] From Kaplan-Meier curve of time to progression (12-week confirmation).

Safety

Studies providing evaluable safety data

The sponsor performed an integrated safety analysis based on 3 placebo-controlled studies in MS (Study C1900, Study 301 and Study 302), which were combined into Pool A. The sponsor also considered the broader population of patients from extension studies, including the second part of C1900 and Study 303, which was the open-label extension of the pivotal studies. These were combined into Pool B. The Pool B data is more meaningful, because active treatment can be compared with placebo but the Pool B data covers a longer period of treatment, up to 5 years, and a greater number of patients, because previous placebo recipients switched to active treatment.

Table 14. Pools for integrated safety analysis in MS.

Pool	Study (Duration)	Treatment Groups (N[a])	Pooled Treatment Groups (N[b])
Pool A Placebo-Controlled Studies	C-1900 (Part 1) (6 Months)	Placebo (65) BG00012 120 mg QD (64) 120 mg TID (64) 240 mg TID (63)	Placebo: 65+408+363=836 BG00012 Lower Doses: (120 QD and 120 TID): 64+64=128 BG00012 240 mg BID: 410+359=769 BG00012 240 mg TID: 63+416+344=823 Total BG00012: 1720 GA: 351
	109MS301 (2 Years)	Placebo (408) BG00012 240 mg BID (410) 240 mg TID (416)	
	109MS302 (2 Years)	Placebo (363) BG00012 240 mg BID (359) 240 mg TID (344) GA (351)	
Pool B Placebo-Controlled and Uncontrolled Studies (Includes 1720 BG00012-treated subjects from Pool A + 748 newly treated subjects from uncontrolled extension studies)	C-1900 (Part 2) (6 Months)	BG00012 →BG00012[c] (166) 120 mg QD (58) 120 mg TID (56) 240 mg TID (52) Placebo →BG00012 240 mg TID (59)	BG00012 Lower Doses (120 mg QD and 120 mg TID)=128 (from Pool A) BG00012 240 mg BID: 769 (from Pool A)+238+106=1113 BG00012 240 mg TID: 823 (from Pool A)+59+236+109=1227 Total BG00012: 2468
	109MS303 (up to 5 Years)[d]	BG00012 →BG00012 (956) 240 mg BID (477) 240 mg TID (479) Placebo/GA →BG00012 240 mg BID (238/106) Placebo/GA →BG00012 240 mg TID (236/109)	

[a] Represents the number of subjects in the safety population of each study.
[b] Represents the number of subjects in the safety population for integrated analysis.
[c] Subjects continued on the same dose from the parent study.
[d] Study 303 was ongoing at the time of this submission. Data collected as of 03 August 2011 were included in the Pool B integrated analysis.

A small number of subjects were also assessed in the sponsor's Clinical Pharmacology program, and in studies of psoriasis and rheumatoid arthritis (see below).

In all of the studies contributing to Pool A, a standard approach was taken to collect safety data. Adverse events were detected during routine scheduled consultations and when patients had unscheduled presentations to their doctor or Emergency Department. Standard monitoring for abnormalities in laboratory tests was performed at regular intervals.

Patient exposure

Patient exposure to BG00012 in MS studies is summarised in Table 15 below. Exposure in psoriasis studies is shown in Table 16 and in the Clinical Pharmacology program in Table 17. Exposure in patients with rheumatoid arthritis was limited: 101 subjects were exposed to BG00012 and 51 subjects were exposed to placebo in Study 109RA201. These treatments were administered with methotrexate, which potentially confounds the assessment of safety because of its own adverse event profile.

Table 15. MS Studies included in the summary of safety.

Study Category	Phase Duration	Number Dosed			Comments
		Placebo	GA	BG00012	
Placebo-controlled Studies					
C-1900 (*Part 1*)[a]	Phase 2 24 weeks	65	--	191	These studies form the cohort of subjects participating in placebo-controlled studies in RRMS
109MS301	Phase 3 96 weeks	408	--	826	
109MS302	Phase 3 96 weeks	363	351	703	
Uncontrolled Studies					
C-1900 (*Part 2*)[a]	Phase 2 24 weeks	--		59	These 2 extension studies together with the placebo-controlled studies form the cohort of subjects to study longer-term use of BG00012
109MS303[b]	Phase 3 5 years (ongoing)	--		689	
109MS201	Phase 2 32 weeks (ongoing)	--		44	Add-on study of IFN-β or GA plus BG00012. Data have not been integrated but are described in Section 5.9.1.
Clinical Pharmacology Studies					
109MS101	Phase 1 24-hour dosing period	--		48	PK study of primary metabolite (MMF) of BG00012. Data have not been integrated but are described in Section 1.1.9.2.

[a] Study C-1900 consisted of a placebo controlled phase (Part 1) and a dose-blind safety extension phase (Part 2). A total of 225 subjects enrolled in Part 2 of the study; 59 of these subjects were newly treated with BG00012 having received placebo in Part 1 of the study.
[b] The open-label extension Study 303 enrolled subjects who had completed the pivotal Phase 3 studies 301 and 302. A total of 1645 subjects enrolled in the study; 689 of these subjects were newly treated with BG00012 having received placebo (N=474) or GA (N=215) in the pivotal studies.

Table 16. Supportive psoriasis studies included in the summary of safety.

Study Category	Phase Duration	Number Dosed		Comments
		Placebo	BG00012	
Placebo-Controlled Studies				
201-WP-12/01 (Part 1)	Phase 2 12 weeks	36	108	These studies form the cohort of subjects participating in short-term placebo-controlled psoriasis studies
201-KG-01/02	Phase 3 16 weeks	70	105	
Uncontrolled Extension Studies				
201-WP-12/01 (Part 2)[a]	Phase 2 24 weeks	--	28	These 2 extension studies together with the placebo-controlled studies form the cohort of subjects that provide longer-term safety data with BG00012 in psoriasis subjects
201-KG-03/03[b]	Phase 3 2 years	--	55	
Clinical Pharmacology Studies				
201-BG-PK-01/02	Phase 2a	--	24	PD study to determine mediators of flushing. Data have not been integrated but are described in Section 1.1.9.3

Note: safety data from psoriasis studies were not integrated with data from studies in MS.
[a] Study 12/01 consisted of a placebo controlled phase (Part 1) and an open-label phase (Part 2). A total of 108 subjects enrolled in Part 2 of the study; 28 of these subjects were newly treated with BG00012 having received placebo in Part 1 of the study.
[b] The open-label extension Study 03/03 enrolled subjects who had completed the Phase 3 Study, KG-01/02. A total of 143 subjects enrolled in the study; 55 of these subjects were newly treated with BG00012 having received placebo in the Phase 3 study.

Table 17.Studies in healthy volunteers included in the summary of safety.

Study	Study Description	Number Dosed	
		Placebo	BG00012
201-FG-PK-02/02	Crossover, food interaction	--	12
C-1903	Crossover, food effect	--	36
201-FG-PK-03/04	Crossover, ascending dose, PK and safety	--	18
IKP/ID32	Placebo-controlled, safety and tolerability	2	6
IKP/ID33	Crossover, ascending-dose	--	15
109HV101	Thorough QT/QTc, placebo- and active-controlled, 4-way crossover	--	54
109HV102	Single-dose, absorption, metabolism, and excretion	--	8
109HV103	Drug interaction, BG00012 and Avonex®, 2-period, crossover	--	26
109HV104	Drug interaction, BG00012 and Copaxone®, 2-period, crossover	--	26
109HV105	2-period, crossover, PK profile, BG00012 standard and API formulations	--	14
109HV106	Placebo-controlled, safety and tolerability, BG00012 with and without aspirin	14	42
109HV107	2-period, crossover, bioequivalence of single capsule containing 240 mg BG00012 vs. 2 × 120 mg capsules	--	81

API = active pharmaceutical ingredient; PK = pharmacokinetic.

For placebo controlled safety data, the duration of exposure is summarised below. Most subjects were followed for ≥ 84 weeks, and about half for ≥ 96 weeks. A total of 769 subjects received the proposed dose (240 mg BID), and 823 received a higher dose (240 mg TID). This represents an adequate exposure for the detection of common adverse events but does not allow assessment of rare side effects, which will require on-going postmarketing surveillance.

Table 18. Overall extent of exposure: controlled MS studies (pool A).

	Placebo	BG00012 Lower Doses (c)	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 weeks on study treatment (a)						
>0 to < 12 weeks	38 (5)	7 (5)	84 (11)	104 (13)	195 (11)	26 (7)
>=12 to < 24 weeks	80 (10)	72 (56)	32 (4)	55 (7)	159 (9)	11 (3)
>=24 to < 36 weeks	66 (8)	49 (38)	23 (3)	48 (6)	120 (7)	8 (2)
>=36 to < 48 weeks	40 (5)	0	29 (4)	16 (2)	45 (3)	12 (3)
>=48 to < 60 weeks	48 (6)	0	21 (3)	21 (3)	42 (2)	7 (2)
>=60 to < 72 weeks	34 (4)	0	15 (2)	15 (2)	30 (2)	9 (3)
>=72 to < 84 weeks	14 (2)	0	14 (2)	16 (2)	30 (2)	9 (3)
>=84 to < 96 weeks	144 (17)	0	177 (23)	144 (17)	321 (19)	68 (19)
>=96 to < 100 weeks	362 (43)	0	361 (47)	389 (47)	750 (44)	185 (53)
>=100 weeks	10 (1)	0	13 (2)	15 (2)	28 (2)	16 (5)
>=12 weeks	798 (95)	121 (95)	685 (89)	719 (87)	1525 (89)	325 (93)
>=24 weeks	718 (86)	49 (38)	653 (85)	664 (81)	1366 (79)	314 (89)
>=36 weeks	652 (78)	0	630 (82)	616 (75)	1246 (72)	306 (87)
>=48 weeks	612 (73)	0	601 (78)	600 (73)	1201 (70)	294 (84)
>=60 weeks	564 (67)	0	580 (75)	579 (70)	1159 (67)	287 (82)
>=72 weeks	530 (63)	0	565 (73)	564 (69)	1129 (66)	278 (79)
>=84 weeks	516 (62)	0	551 (72)	548 (67)	1099 (64)	269 (77)
>=96 weeks	372 (44)	0	374 (49)	404 (49)	778 (45)	201 (57)
n	836	128	769	823	1720	351
Mean	72.49	22.34	76.58	72.28	70.49	81.58
SD	32.556	5.137	33.686	36.366	36.498	29.677
Median	95.71	23.86	95.86	95.86	95.86	96.00
Min, Max	0.7, 103.0	0.7, 24.4	0.1, 102.0	0.1, 110.9	0.1, 110.9	0.1, 104.0
Total number of subject-years exposed to study treatment (b)	1161.50	54.80	1128.69	1140.01	2323.50	548.75

NOTE: Numbers in parentheses are percentages.
(a) Days on study treatment is calculated as (date of last dose - date of first dose) + 1. Missing/partial dates of last dose were imputed. Weeks on study drug is calculated as (days on study drug)/7.
(b) Total number of subject-years exposed to study treatment is calculated as the sum of number of days exposed to study treatment/365.25.
(c) Subjects on BG00012 Lower Doses were dosed for up to 24 weeks only in either placebo-controlled treatment phase or extension phase of C-1900.

Postmarketing experience

There is no postmarketing data available at present. Under "Postmarketing Data", the sponsor states "*BG00012 is an investigational product and has not been approved or marketed in any countries.*"

Safety issues with the potential for major regulatory impact

Liver toxicity

Abnormal liver function tests (LFTs) are occasionally observed with BG00012 treatment but serious liver toxicity was not observed in the study program. The draft PI does not explicitly recommend monitoring of LFTs in BG00012 recipients but reports that LFTs were occasionally abnormal. This seems appropriate. The potential for rarer, more severe reactions will need to be the subject of specific postmarketing surveillance strategies.

Haematological toxicity

BG00012 treatment is associated with a reduction in total white cell counts and lymphocyte counts. One case of Grade 4 lymphopaenia was observed in the pivotal studies, in a recipient of BG00012 at the proposed dose but this was not associated with any clinical sequelae. Haematological monitoring should be recommended in the PI and the potential for more serious toxicity should be the subject of specific postmarketing surveillance.

Serious skin reactions

BG00012 treatment is associated with an increased incidence of skin reactions, including rash, but only one recipient of BG00012 had a SAE related to skin, comparable to the one skin-related SAE reported in a placebo recipient.

Cardiovascular safety

BG00012 does not appear to pose a significant risk of cardiovascular events. It is associated with marked flushing, however, indicating vasodilation that might be symptomatic in at risk individuals.

Unwanted immunological events

BG00012 does not appear to be associated with a substantial risk of unwanted immunological events.

Evaluator's overall conclusions on clinical safety

The overall safety profile of BG00012 was considered to be acceptable. Its use is associated with mild to moderate changes in LFTs, and reductions in total white cell count and lymphocyte count but these changes were not of major clinical significance in the pivotal studies. It remains unclear whether some subjects will be at risk of more substantial hepatic or haematological toxicity and this will need to be monitored in the postmarketing context.

Severe adverse events were relatively rare with BG00012 and the spectrum of events was not qualitatively different to those seen with placebo.

BG00012 is also associated with a range of tolerability issues, particularly flushing, which was seen in ~30% of subjects, and gastrointestinal intolerance, which was seen in more than 25% of subjects in the first month. Both of these problems were reported less commonly with continued follow-up but it is unclear if the symptoms actually improved. Discontinuations due to flushing were seen in ~3% of subjects and due to GI intolerance in ~4% of subjects.

List of questions

Efficacy

The sponsor should clarify the source of the cited "relative risk reductions" in the proposed PI and the sponsor's Summary of Clinical Efficacy, as discussed previously.

In particular, the sponsor should answer the following questions:

- In Study 301, what was the cumulative relative risk reduction for the primary endpoint of "*proportion of subjects relapsed*"?
- Do the percentages cited in the following statement actually refer to instantaneous hazard reduction? *"This indicated the risk of relapse at 2 years was reduced by 49% (p <0.0001) and 50% (p <0.0001) following treatment with BG00012 BID and TID, respectively, compared with placebo"*.

Safety

The sponsor should clarify the category of risk for use in pregnancy.

Clinical summary and conclusions

First Round Benefit/Risk Assessment

First round assessment of benefits

The efficacy of BG00012 in the RRMS population, as demonstrated in the two pivotal studies (Study 301 and Study 302), is summarised in the table below.

Table 19. Pivotal phase III studies 301 and 302 individual efficacy results at 2 years.

Study 301				Study 302				
Endpoint	Placebo	240 mg BID	240 mg TID	Endpoint	Placebo	240 mg BID	240 mg TID	GA
Primary								
Proportion relapsing[1]	0.461	0.270 p<0.0001[a]	0.260 p<0.0001[a]	Annualized relapse rate	0.401	0.224 p<0.0001[b]	0.198 p<0.0001[b]	0.286 p=0.0128[b]
Secondary (listed in descending rank order)								
New or newly enlarging T2 hyperintense lesions (adjusted mean number)	17.0	2.6 p<0.0001[b]	4.4 p<0.0001[b]	New or newly enlarging T2 hyperintense lesions (adjusted mean number)	17.4	5.1 p<0.0001[b]	4.7 p<0.0001[b]	8.0 p<0.0001[b]
GdE lesions (mean number)	1.8 [c]	0.1 p<0.0001[c]	0.5 p<0.0001[c]	New T1 hypointense lesions (adjusted mean number)	7.0	3.0 p<0.0001[b]	2.4 p<0.0001[b]	4.1 p=0.0021[b]
Annualized relapse rate	0.364	0.172 p<0.0001[b]	0.189 p<0.0001[b]	Proportion relapsing[1]	0.410	0.291 p=0.0020[a]	0.241 p<0.0001[a]	0.321 p=0.0097[a]
Disability progression (proportion progressing[2])	0.271	0.164 p=0.0050[a]	0.177 p=0.0128[a]	Disability progression (proportion progressing[2])	0.169	0.128 p=0.2536[a]	0.130 p=0.2041[a]	0.156 p=0.7036[a]
Tertiary								
New T1 lesions (adjusted mean number)	5.6	1.5 p<0.0001[b]	2.1 p<0.0001[b]	Gd+ lesions mean number)	2.0	0.5 p<0.0001[c]	0.4 p=0.0001[c]	0.7 p=0.0003[c]

NOTE: All p-values compare each active treatment group versus placebo based on [a] Cox proportional hazards model; [b] negative binomial regression; [c] ordinal logistic regression.

[1] From Kaplan-Meier curve of time to relapse.
[2] From Kaplan-Meier curve of time to progression (12-week confirmation).

The benefits of BG00012 in the proposed usage are:

- A reduction in relapses, manifested as a reduction in the proportion relapsed after two years of treatment and a reduction in annualised relapse rate.
- For Study 301, the Kaplan-Meier estimate of the proportion of subjects relapsed at 2 years was 27.0% in the BG00012 BID group, compared to 46.1% in the placebo group, a relative reduction of 41%.
- For Study 302, the proportion of subjects who relapsed at 96 weeks was 0.410 in the placebo group compared to 0.291 in the BG00012 BID group. This is equivalent to a relative reduction in two-year risk of 29%.
- Annualised relapse rate was reduced by about half. In Study 301, the annualised relapse rate in the placebo group was 0.364 relapses/year and in the BG00012 240 mg BID group it was 0.172 relapses/year, a 53% reduction. In Study 302, the adjusted annualised relapse rate was 0.401 in the placebo group, compared with 0.224 in the BG00012 BID group, a relative reduction of 44.0%. The differences with placebo were highly significant.
- A substantial decrease in MRI activity for a number of MRI measures, as summarised in the table above.
- Reduced progression, as measured in terms of the EDSS and the MSFC.
- An efficacy that appears to be at least as good as an existing agent, glatiramer acetate.
- An oral route of administration.

- Apparent cardiovascular safety, which may provide an alternative for subjects in whom fingolimod is contraindicated because of cardiac risk.

First round assessment of risks

The risks of BG00012 in the proposed usage are:

- Leukopenia and lymphopaenia
- Abnormal liver function tests

Tolerability issues in many patients, particularly related to flushing and gastrointestinal symptoms

First round assessment of benefit-risk balance

The benefit-risk balance of BG00012, given the proposed usage, was considered to be favourable.

Second round evaluation of clinical data submitted in response to questions

The sponsor has responded to two clinical issues raised in the First Round Clinical Evaluation: the conflation of hazard ratios and cumulative risk reduction (see above). The sponsor has also responded to a first round criticism of one sentence in the proposed PI; this issue was not submitted as a clinical question.

Hazard ratios versus cumulative risk reduction

The nature of the problem and the sponsor's response

The sponsor was asked to respond to the multi-part question posed above and was given copies of the relevant sections of the first round evaluation report to provide context for the question. The main issue of concern was that several quantitative treatment effects cited by the sponsor as "relative risk reductions" had values that appeared to be based on *hazard ratios* but were presented in the sponsor's primary study reports and proposed PI without any direct reference to hazard ratios. Instead, the sponsor's wording was ambiguous or misleading, with the results described in a way that appeared to refer to cumulative risk reduction or the overall proportion of patients relapsed. This had the effect of inflating the apparent magnitude of the treatment benefit.

The sponsor's response, which will be discussed in detail below, confirms that hazard reductions were indeed used as the basis for *"relative risk reductions"* throughout the submission, though the sponsor disputes that this method of reporting is erroneous or misleading.

The sponsor states: *"These results are based on the reduction in hazards (i.e. "1" minus the hazard ratio) and are extracted directly from the pre-specified analysis in the statistical analysis plan…"*

After an explanation of how the hazard ratios were derived, the sponsor went on to say:

"In relation to this, we also note that the evaluator states on page 20 of the consolidated set of questions: "…from the table above, the two-year risk estimated by the Kaplan-Meier method was only reduced by 41% and 44%, suggesting that the sponsor is in error, misreporting the reduction in instantaneous hazard risk as a reduction in cumulative two-year risk." Given the explanation above, we advise that there was no error but concede the needs [sic] to have clearer label [sic] of the expression of risk reduction, based on the pre-specified statistical analysis plan for Study 301."

From the evaluator's perspective, this remains an important issue, and conflating hazard reductions with risk reductions is a serious error.

The sponsor's submission included the following statement:

"This indicated the risk of relapse at 2 years was reduced by 49% (p <0.0001) and 50% (p <0.0001) following treatment with BG00012 BID and TID, respectively, compared with placebo".

This wording strongly implies that the cited values refer to the risk of a patient relapsing over the course of two years; that is, the risk of finishing the two year period in the relapsed sub-group, as compared to the non-relapsed subgroup. This risk can be referred to more clearly as the *cumulative two-year risk of relapsing*; it has a natural, intuitive, common sense meaning that is transparent to patients and clinicians. A patient would like to know "I*f I do not take treatment for the next two years, what is the probability (risk) I will have a relapse, and what is the probability I will remain relapse-free? Conversely, if I take the drug, how much will those probabilities change?*" The underlined statement from the sponsor's study report implies that the probability of being in the relapsed group, at the two year time point, was *halved* by active treatment; reduced by 50% with one dose and by 49% with another. This interpretation is also favoured by the sponsor's description of the primary endpoint as "*the proportion of subjects relapsed*", which refers to an overall *proportion* of subjects after two years of treatment, not to a *rate*. Without additional context or mention of hazard ratios, very few readers would guess that the risk of being in the relapsed group at two years was reduced by substantially *less than* 50%.

Hazards and hazard ratios are abstract concepts and the associated terminology is unfamiliar to most patients and clinicians outside academic settings. Hazard refers to the instantaneous risk of a bad event, which can have a straightforward interpretation in some contexts but tends to be confusing in other contexts, particularly when the "bad event" can only occur once to each subject (as in the case of a first MS relapse on treatment), so that *the number of subjects at risk does not equal the number of subjects on treatment.*

There is nothing intrinsically wrong with estimating treatment benefit in terms of instantaneous hazard reductions or hazard ratios. Hazard reductions can be derived directly from the Cox proportional hazard model and have a clear mathematical meaning. Care must be taken in reporting hazards, though, and in distinguishing them from the common-sense notion of overall (cumulative) risk reduction over a specified time period. Although the sponsor has now clarified the matter, the sponsor's original submission did not take the necessary care to report these results clearly and instead used wording that was misleading.

The sponsor has since confirmed that the cumulative two year risk reductions were substantially less than the values originally cited for "*risk of relapse at 2 years*".

"In Study 301, the "relative reduction" for the primary endpoint of "proportion of subjects relapsed", based on the Kaplan-Meier estimate at 2 years, are 41% and 44% for the BG00012 240 mg BID and TID groups respectively. In Study 302, the relative reductions are 29%, and 41% for the BG00012 240 mg BID, and TID groups respectively."

These percentages are substantially less impressive than the apparent 49-50% benefit originally cited by the sponsor.

To see why the sponsor's claims are misleading, it is helpful to review the main reason why the hazard reductions and the cumulative risk reductions are numerically different.

The sponsor explains the hazard analysis as follows:

"This statistical analysis used the Cox "proportional hazards" model, which adjusted for covariates of age (<40 vs. >=40 yrs), region, baseline EDSS score (<=2.0 versus >2.0), and number of relapses in the year prior to study entry. The Cox model takes into account the data from all subjects who experienced relapses, as well as those who were relapse-free (censored due to the fact that the patients were relapse-free at two years), and the timing of the relapse and censoring over the course of the study."

Although the Cox proportional hazards model introduces some adjustments according to the baseline stratification factors listed, these adjustments could also be applied to cumulative two-year risk, and minor statistical adjustments are not the chief source of the large numerical difference between hazard reductions and cumulative risk reductions. Instead, the difference arises from the nature of instantaneous risk versus cumulative risk, and most importantly from the number of subjects at risk. Hazard reductions can diverge markedly from cumulative risk reductions when the hazardous events being counted can only occur once, as in the current submission. The primary endpoint in Study MS301 was "*the proportion of subjects relapsed at 2 years*" (actually, 96 weeks). This endpoint necessarily splits subjects into two mutually exclusively categories: those who have relapsed and those who have not. Once a subject has entered the "relapsed" group, they cannot leave that group and are not at risk of entering it again, and thus they face no further hazard for this endpoint. The hazard ratio only applies to subjects remaining at risk, and so relapsed subjects are, in effect, censored from the remainder of the analysis. Such subjects, which can be considered treatment failures for the primary endpoint, stay in the treated cohort and dilute the overall cumulative benefit of a two year course of treatment but they are removed from further hazard analysis. (Such subjects can experience a potential treatment benefit for other endpoints, such as the overall annualised relapse rate but they cannot experience further benefit or harm for the primary endpoint.)

The sponsor's response explains the discrepancy somewhat differently, by referring to the risk faced by non-relapsed subjects.

"Since the Cox model assumes a constant hazard ratio over time, the risk reduction relative to placebo will not change over time. In other words, if a subject did not experience a relapse over the course of the 2 year period, the risk of relapse was reduced by 49% and 50% for BG00012 240 mg BID and TID group, respectively (based on Study 301 data) and 34% and 45% for the BG00012 240 mg BID and TID groups, respectively (based on Study 302 data)."

This statement is confusing, though it probably alludes to the fact that the subjects at risk are a progressively shrinking cohort and it is this cohort that enjoyed the ~50% hazard reduction in Study 301. The comment "*if a subject did not experience a relapse over the course of the 2 year period, the risk of relapse was reduced by X*" is almost meaningless, because such subjects *by definition* have avoided a relapse entirely; if they could be identified prospectively at baseline, their risk would be zero and if they have only been identified in retrospect, the notion of risk for the two year period barely applies. They cannot be at risk of an event in the past, much less an event which is known not to have happened. What the sponsor is probably trying to say is that a non-relapsed subject's instantaneous risk of a relapse, at any time moving forward, was 49% and 50% of the placebo risk in Study MS301, for the two doses respectively. This estimate of instantaneous risk applies to the progressively shrinking *non-relapsed* subgroup at any stage of the study but is increasingly at odds with the cumulative benefit displayed by the larger, overall study population (which includes rather than censors the treatment failures).

The group of treatment failures necessarily enlarges with longer periods of follow up, even when relative hazard reductions remain constant, so cumulative relative risk reductions will tend to deteriorate with longer periods of follow-up and progressively more conversions to the studied endpoint, leading to progressively greater divergence from instantaneous hazard reductions. Over the course of the two-year study MS301, the divergence was ~8% for the proposed dose (49% versus 41%). Eventually, if the study cohort were followed until 90% of actively treated subjects had relapsed the *cumulative*

relative risk reduction would necessarily be ≤10%[33], even if the hazard ratio had remained at 50% throughout the period of risk. This dependency on length of follow up is not an ideal property for a measure of treatment benefit, and is one reason why hazard ratios may be favoured in academic settings but it is a property that is intuitively known to clinicians and *factored in when assessing claims of relative benefit for a given time period.*

The problem, then, is not the sponsor's use of hazard ratios, but the manner in which they have been reported, using wording that could apply to cumulative risk reduction. If a clinician reads that the risk of relapsing after two years is halved by active treatment, the clinician will think, quite reasonably, that an untreated cohort will have twice as many relapsed subjects after two years as a treated one, and communicate this erroneous interpretation to the patient. The sponsor has a responsibility to prevent such errors.

Note that, even for clinicians who are familiar with hazard ratios and the way that they differ from cumulative risk reduction, there is a risk of conflating the two measures *unless the sponsor is clear in reporting the results.* Just as a hazard reduction of ~49% can be associated with a cumulative two year risk reduction of only ~41% (as demonstrated in Study MS301), the hazard reduction required to produce a true 49% reduction in cumulative risk over two years would be expected to be *greater than* 49%, given similar baseline placebo risk. This means that even a clinician aware of hazard ratios could be misled by the sponsor's claims, inferring that active treatment confers a hazard reduction substantially better than 49%.

The safest approach in reporting such results is to report both measures (hazard reduction and cumulative risk reduction) and to label each measure clearly. If only one measure of risk reduction is to be reported, then the commonsensical and clinically transparent measure of cumulative risk reduction is less misleading than the superficially more impressive hazard reduction, particularly when the stated endpoint refers to "proportion relapsed" rather than to a rate.

Conventions in reporting hazard ratios

In a couple of sections of their response to the first round questions, the sponsor argued that hazard ratios are a standard way of reporting MS endpoints.

"Although the concept of "instantaneous hazard reduction" is mathematically correct, it is not usually interpreted as such in MS clinical trials, for ease of understanding to the general readers."

"The Cox model is a conventional method utilized to analyze time to disability progression and reduction in proportion of subjects progressed in Phase III MS trials such as those for natalizumab (Tysabri), fingolimod (Gilenya), laquinimod, teriflunomide (Aubagio). The reductions in hazard, are commonly referred to as the reductions in risk of progression relative to placebo in official publications of the study results (References: Polman et al 2006, Kappos et al 2010, Giovannoni et al 2010 and Comi et al 2012). In addition, relative reductions are presented in the TGA approved Product Information (summary of clinical efficacy) for Tysabri and Gilenya for the disability progression or Annualised Relapse Rate (ARR) endpoint."

Even if it is accepted that hazard ratios are a standard method of reporting MS studies, it does not follow that hazard ratios should be reported without explicitly labelling them. The majority of the references mentioned by the sponsor above make frequent use of hazard ratios but these are reported clearly as such. An example is shown below, from a reference supplied by the sponsor (*Comi et al 2012*).

[33]A 10% relative risk reduction would apply to the situation where 100% of placebo recipients and 90% of active recipients had relapsed; if less than 100% of placebo recipients had relapsed, the relative benefit would be less than 10%.

Table 20. From Comi *et al* 2012. Clinical and MRI end points.

End Point	Laquinimod (N=550)	Placebo (N=556)	P Value
Relapse			
Annualized relapse rate			
Adjusted mean	0.30±0.02	0.39±0.03	0.002†
Risk ratio (95% CI)	0.77 (0.65 to 0.91)		
Relapse-free during study			
Adjusted proportion (%)	62.90	52.24	<0.001‡
Odds ratio (95% CI)	1.55 (1.20 to 1.99)		
Annualized rate of relapses requiring hospitalization or IV glucocorticoids			
Adjusted mean	0.24±0.02	0.33±0.02	<0.001†
Risk ratio (95% CI)	0.72 (0.61 to 0.86)		
Disability			
Risk of disability progression confirmed at 3 mo			
Hazard ratio (95% CI)	0.64 (0.45 to 0.91)		0.01§
Patients with confirmed disability progression (%)	11.1	15.7	
Risk of disability progression confirmed at 6 mo			
Hazard ratio (95% CI)	0.51 (0.34 to 0.79)		0.002§
MSFC — total z score at 24 mo, including discontinuation after 12 mo¶			
Mean (95% CI)	0.06 (0.00 to 0.11)	0.04 (−0.02 to 0.09)	0.59‖
Lesion activity on brain MRI			
Cumulative no. of gadolinium-enhancing lesions at 12 and 24 mo			
Mean	1.33±0.14	2.12±0.22	<0.001**
Rate ratio (95% CI)	0.63 (0.49 to 0.81)		
Cumulative no. of new or enlarged lesions on T_2-weighted images at 12 and 24 mo			
Mean	5.03±0.08	7.14±0.07	<0.001**
Rate ratio (95% CI)	0.70 (0.58 to 0.85)		
Change in brain volume from baseline to 24 mo			
Adjusted mean percent change	−0.87	−1.30	<0.001††
Adjusted mean percentage-point difference (95% CI)	0.43 (0.27 to 0.59)		

On the other hand, the sponsor is correct in pointing out that the approved PI for Tysabri appears to set a precedent for using the term '*Relative Risk Reduction*' to present hazard reductions. The tables below are copied from the online digital PI for Tysabri; only the clinical section of each table is shown. (<http://www.biogenidec.com.au/Admin/Public/DWSDownload.aspx?File=%2fFiles%2fFiler%2fAustralia%2fTysabri-PI-19-NOV-2012.doc>).

In the monotherapy Tysabri study (Table 21 below), the reported relative risk reduction in sustained disability is 42%, which is within 1% of the relative reduction (41.4%) that would be calculated from direct inspection of percentage of patients with sustained increase in disability at two years (17/29 = 0.586, that is, 17 is 58.6% of 29, so 17% is 41.4% less than 29%). The minor discrepancy could be due to rounding. In the add-on study (Table 22), however, the reported relative risk reduction is 24%, which is greater than the relative reduction (20.7%) deduced from direct inspection (23/29 = 0.793, that is, 23 is 79.3% of 29, so 23% is 20.7% less than 29%). This discrepancy suggests that the Tysabri PI should be modified to improve clarity along the same lines as suggested for Tecfidera.

Table 21. Clinical and MRI endpoints in study 1 (monotherapy study) at 2 years.

	TYSABRI n=627	Placebo n=315
Clinical Endpoints		
Percentage with sustained increase in disability	17%	29%
Relative Risk Reduction	42% (95% CI 23%, 57%)	
Annualised relapse rate	0.23	0.73
Relative reduction (percentage)	68% (95% CI 60%, 74%)	
Percentage of patients remaining relapse-free	67%	41%
MRI Endpoints		
New or newly enlarging T2-hyperintense lesions		
Median	0	5
Percentage of patients with:*		
0 lesions	57%	15%
1 lesion	17%	10%
2 lesions	8%	8%
3 or more lesions	18%	68%

Table 22. Clinical and MRI endpoints in study 2 (add-on study) at 2 years.

	TYSABRI plus AVONEX n=589	Placebo plus AVONEX n=582
Clinical Endpoints		
Percentage with sustained increase in disability	23%	29%
Relative Risk Reduction	24% (95% CI 4%, 39%)	
Annualised relapse rate	0.34	0.75
Relative reduction (percentage)	55% (95% CI 47%, 62%)	
Percentage of patients remaining relapse-free	54%	32%

The PI for Gilenya on the other hand, sets a precedent for explicit acknowledgement of hazard ratios when these are used, as shown in the table below. Note that the percentage of patients remaining relapse-free was a major endpoint in the Gilenya study (as in the Tecfidera study), but this percentage is reported in the Gilenya PI directly, rather than as a hazard ratio.

Table 23. Clinical and MRI results of study D2301.

	GILENYA 0.5 mg	GILENYA 1.25 mg	Placebo
Clinical Endpoints	N=425	N=429	N=418
Annualized relapse rate	0.18	0.16	0.40
(primary endpoint)	(p<0.001*)	(p<0.001*)	
Relative reduction (percentage)	54	60	
Percent of patients remaining	70.4	74.7	45.6
relapse-free at 24 months	(p<0.001*)	(p<0.001*)	
Risk of disability progression			
Hazard ratio (95% CI)	0.70 (0.52, 0.96)	0.68 (0.50, 0.93)	
(3-month confirmed)	(p=0.024*)	(p=0.017*)	
Hazard ratio (95% CI)	0.63 (0.44, 0.90)	0.60 (0.41, 0.86)	
(6-month confirmed)	(p=0.012*)	(p=0.006*)	
MRI Endpoints			
Number of new or newly enlarging	n=370	n=337	n=339
T2 lesions			
Median (mean) number over 24 months	0.0 (2.5)	0.0 (2.5)	5.0 (9.8)
	(p<0.001*)	(p<0.001*)	
Number of Gd-enhancing lesions	n=369 (Month 24)	n=343 (Month 24)	n=332 (Month 24)

Overall, the majority of MS studies using hazard ratios have been explicit when reporting their results. The Tysabri PI is an exception, in that it does *not* clearly indicate that the relative risk reduction in disease progression has been expressed in terms of hazard ratios but this is an argument in favour of fixing the Tysabri PI rather than repeating the error with Tecfidera.

The most common endpoint for disease modifying agents in MS is annualised relapse rate, rather than proportion relapsed. Relapse rates are appropriately expressed as hazard ratios. Given that relapse rates are necessarily expressed as events per time, and relapses contributing to these rate estimates do not have the property of removing subjects from the cohort at risk, there is relatively little chance of confusing the reader with hazard ratios when the primary endpoint is relapse rate. The problem arises from the sponsor's description of the primary endpoint as "*proportion relapsed*" at the end of two years, followed by numerical data based on instantaneous hazard rates. Referring to the proportion of subjects relapsed at two years creates the expectation that what is being reported as "*relative risk*" is the relative proportions of patients reaching the relapsed subgroup at two years, which is the same as the cumulative relative risk over two years. Inserting an unexpected hazard ratio as the means of reporting this change in proportions is misleading, and inflates the apparent benefit of the treatment.

The sponsor's proposed changes to the PI to address the issue

The sponsor indicates that the relative reductions in proportions relapsed were as follows:

"In Study 301, the "relative reduction" for the primary endpoint of "proportion of subjects relapsed", based on the Kaplan-Meier estimate at 2 years, are 41% and 44% for the BG00012 240 mg BID and TID groups respectively. In Study 302, the relative reductions are 29%, and 41% for the BG00012 240 mg BID, and TID groups respectively."

Unfortunately, the sponsor has not indicated a readiness to include these new estimates of risk reduction within the revised PI. Instead, they propose use of the following revised table (truncated copy):

Table 24. Clinical and MRI results of study 1.

	TECFIDERA 240 mg BID (n=410)	Placebo (n=408)	P-value
Clinical Endpoints			
Annualised relapse rate	0.172	0.364	<0.0001
Relative reduction (percentage)	53%		
(95% CI)	(39%, 64%)		
Proportion of subjects relapsed	0.270	0.461	
Risk of relapse			
Hazard Ratio	0.51		<0.0001
(95% CI)	(0.40, 0.66)		
Relative reduction (a)	49%		
(95% CI)	(34%, 60%)		
Proportion with disability progression	0.164	0.271	
Risk of disability progression			
Hazard Ratio	0.62		
(95% CI)	(0.44, 0.87)		0.0050
Relative reduction (a)	38%		
(95% CI)	(13%, 56%)		

Compare the revised table, above, to the version that was discussed in the first round evaluation, reproduced below:

Table 25. Clinical and MRI results of study 1.

	NEUTRINZA 240 mg BID (n=410)	Placebo (n=408)	P-value
Clinical Endpoints			
Annualised relapse rate	0.172	0.364	<0.0001
Relative reduction (percentage)	53%		
(95% CI)	(39%, 64%)		
Proportion relapsing	0.270	0.461	<0.0001
Relative risk reduction	49%		
(95% CI)	(34%, 60%)		
Proportion with disability progression	0.164	0.271	0.0050
Relative risk reduction	38%		
(95% CI)	(13%, 56%)		

The revised version is an improvement, because the term "*Relative risk reduction*" no longer appears immediately under the heading "*Proportion relapsing*", an arrangement that strongly implied that the cited reduction was a relative reduction in the proportion relapsing. The term "*Relative reduction (a)*" now appears under the ambiguous heading "*Risk of relapse*", which refers to the hazard rate but could easily be assumed to refer to the risk of (at least one) relapse over the course of the study. The bracketed footnote marker "*(a)*" refers the reader to a footnote at the end of the table, which in turn explains that the figure cited is based on the hazard ratio but the footnote is found on the next page. Furthermore, the cited risk reduction adds no new or useful information, because it is simply the complement of the hazard ratio (it is 1-hazard ratio, expressed as a percentage); the same relation holds for the 95%CIs (34% is the complement of 0.66, 60%

the complement of 0.40, 13% the complement of 0.87, and so on). That is, those who know what the "*risk reduction*" means in this context could derive it easily for themselves, by subtracting from 100%; those who do not know what it means might assume it refers directly to the primary endpoint of the study, the proportion relapsing.

A potentially clearer version of the table, produced by the evaluator, is shown below (Table 26). The lines that appear in red, italics and underlined correspond to the "r*elative reduction (a)*" in the sponsor's proposed table. They add no new information and would be better omitted but at least the version below clearly distinguishes the reduction in proportion of relapsed patients (41%) from the relative reduction in hazard (49%). The 41% figure in the table was derived directly from the cited proportions (0.270 is ~59% of 0.461, implying it has been reduced by ~41%) but this is similar to the risk estimated by the Kaplan-Meier approach, provided by the sponsor above. (*"In Study 301, the "relative reduction" for the primary endpoint of "proportion of subjects relapsed", based on the Kaplan-Meier estimate at 2 years, are 41% and 44% for the BG00012 240 mg BID and TID groups respectively. In Study 302, the relative reductions are 29%, and 41% for the BG00012 240 mg BID, and TID groups respectively."*). If the sponsor preferred to use a Kaplan-Meier estimate of the cumulative two year risk in the PI, instead of directly comparing the proportions relapsed, that approach would also be reasonable; in that case, a footnote of explanation below the table would be appropriate.

Table 26. Clinical and MRI results of study 1.

Clinical Endpoints	Tecfidera 240 mg BID (n=410)	Placebo (n=408)	P-value
Annualised relapse rate	0.172	0.364	<0.0001
Relative reduction (percentage)	53% (95% CI) (39%, 64%)		
Proportion of subjects relapsed	0.270	0.461	
Relative reduction in proportion relapsed	41%		
Hazard Ratio for first relapse (95%CI)	0.51 (0.40, 0.66)		<0.0001
Relative hazard reduction (95%CI)	***49% (34%, 60%)***		
Proportion with disability progression	0.164	0.271	
Relative reduction in proportion progressing	39%		
Hazard Ratio for progression (95% CI)	0.62 (0.44, 0.87)		0.0050
Relative hazard reduction (95%CI)	***38% (13%, 56%)***		

Throughout their submission, the sponsor has taken a similar approach to the risk of disability progression as they took with proportion relapsed, referring in some places of the study reports and PI to the proportion progressing over two years, then slipping into a

comparison of hazard ratios, usually without explicitly noting that the cited figures have been derived from hazard ratios. In principle, all the same arguments apply to this endpoint, and the need for clarity remains important, but for this endpoint the actual numerical difference between the two methods of reporting is relatively minor.

Overall conclusion about the sponsor's response to hazard ratios

The sponsor has confirmed the evaluator's suspicions that values cited in the study reports and proposed PI as "*relative risk reductions*" actually refer to (instantaneous) hazard reductions. The proposed changes in the PI are improvements over the original version but do not go far enough in clarifying the true nature of the data. The sponsor should change all references to "*relative reduction*" or "*relative risk reduction*" throughout the PI to more explicit terminology that directly refers to hazard ratios. This includes the text of the PI and tables including the results for Study 302.

The sponsor should also explicitly report the relative reduction in the proportion of patients relapsed and the relative reduction in the proportion of patients progressed, so that clinicians can predict the likely effects of treating subjects for two years. The study design and the endpoints as described lend themselves naturally to such a description of cumulative risk. A statement such as the following should appear in the PI:

"In Study 301, the relative reductions for the primary endpoint of proportion of subjects relapsed, based on the Kaplan-Meier estimate at 2 years, were 41% and 44% for the Neutrinza [Tecfidera] 240 mg BID and TID groups respectively. In Study 302, the relative reductions were 29% and 41% for the Neutrinza [Tecfidera] 240 mg BID, and TID groups respectively."

Similar statements should be added referring to the proportion of patients progressing.

Pregnancy category

At the time of the first round submission, the sponsor had not decided upon a pregnancy risk category in the proposed PI and the sponsor was asked to clarify this. The sponsor's response is as follows:

> *"No formal studies of BG-12 in pregnant women have been performed.*
>
> *"As of 02 January 2013, there have been 56 pregnancies in the BG00012 clinical development program, of which 38 pregnancies (68%) were reported in subjects exposed to BG00012 (37 subjects with MS and 1 healthy volunteer). Pregnancy outcomes were known for 34 of the 38 BG00012-exposed subjects (89%) 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 fetal abnormalities (i.e., congenital defects) have been reported for any of the pregnancies in the BG00012 clinical development program. The incidence of spontaneous abortion among pregnancies with known outcome was: 3 out of 34 subjects with known outcomes (9%) in the BG-12 treated subjects and 3 out of 14 subjects (21%) in the placebo treated subjects indicating a slightly higher incidence of spontaneous abortion in the placebo arm.*
>
> *"The rates of spontaneous abortion in the BG00012 and placebo-treated subjects are consistent with the expected rate of early pregnancy loss in the general population. Based on the current data, there is no evidence of increased risk of foetal abnormalities or adverse pregnancy outcomes associated with gestational exposure to BG00012 during the first trimester. Reproductive studies in rodents and rabbits showed no evidence of teratogenic effects of BG00012.*
>
> *"In light of these results, the Applicant proposes a pregnancy category B1."*

This is appropriate. Category B1 applies to drugs that have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed, and where studies in animals have not shown evidence of an increased occurrence of foetal damage.

Revision to the PI

As discussed in the first round evaluation, one sentence of the proposed PI implied that Studies 301 and 302 were more similar than they actually were. The sponsor proposed a change to the text which was found acceptable by the evaluator.

Second round benefit-risk assessment

The overall risk-benefit was not altered by the new information.

Second round recommendation regarding authorisation

Tecfidera (BG00012,) should be approved for marketing once the PI has been modified along the lines discussed above.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Product Review (OPR).

The following table (Table 27) summarises the OPR's evaluation of the RMP, the sponsor's responses to issues raised by the OPR and the second round OPR evaluation of the sponsor's responses.

Table 27. Reconciliation of issues outlined in the RMP report. EU SmPC=European Union Summary of Product Characteristics

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	OPR evaluator's comment
1. The sponsor should be aware that safety considerations may be raised by the nonclinical evaluator through the TGA consolidated request for information and/or the Nonclinical Evaluation Report. It is important to ensure that the information provided in response to these include a consideration of the relevance for the Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, please provide information that is relevant and necessary to address the issue in the RMP.	*'Upon receipt of the Nonclinical Evaluation Report, we agree to review any safety considerations raised for relevance for the Risk Management Plan (RMP) and provide information necessary to address the issue in the RMP.'*	This was considered acceptable.
2. The sponsor should submit a protocol for their planned clinical study in patients between ages of 10 and 17 years old and should provide dates for the planned submission of final data for all studies.	The sponsor states that the protocol planned clinical study in patients between ages of 10 and 17 years old was previously submitted outside the RMP Annex and will be added to Annex 5 of the RMP once finalised. The sponsor states: *'With respect to the request in the RMP evaluation report for planned submission of final study data for the observational study and pregnancy registry dates were provided.*	This was considered acceptable, but it is noted that, as at 07 February 2013, module 1.12.1 does not contain a protocol regarding the planned clinical study in patients between ages of 10 and 17 years old. The sponsor should submit a protocol for their planned clinical study in patients between ages of 10 and 17 years old (as the sponsor has agreed to do).

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	OPR evaluator's comment
3. As the sponsor's RMP submission seem to address risk issues based on the proposed European Union indication which does not include children, it would not be unreasonable for the sponsor to reconsider the proposed Australian indication to restrict the drug to adults.	The sponsor has already provided relevant statements in the 'Precautions' section of the proposed PI.	This was considered acceptable.
4. The sponsor should consider clarifying which type of MS is part of the proposed indication to avoid prescriber misunderstanding and inadvertent off-label use.	The sponsor clarified that the proposed indication of Tecfidera should be in patients with "*relapsing-remitting*" multiple sclerosis. The Product Information (PI) will be modified accordingly to reflect this. As directed by the TGA, a revised PI will be submitted following receipt of the final evaluation reports.	This was considered acceptable.
5. In regard to the proposed routine risk minimisation activities, the Delegate may wish to revise the draft product information document as follows: a. The sponsor should inform prescribers about a potential risk of renal changes, to caution them to appropriately dose patients and to monitor renal function where necessary (or a statement to that effect);	*'The sponsor has listed renal toxicity as a potential human risk, and included the histopathology changes observed in the kidneys of preclinical species in EU SmPC Section 5.3.* *In clinical studies, there has been no increased incidence of renal or urinary events observed with BG00012-treated patients. This is consistent with data from Studies 301 and 302 indicating the absence of a treatment effect on β2-microglobulin (a sensitive urinary biomarker for tubular dysfunction) over 3.5 years of dosing. Additional analyses of the estimated glomerular filtration rate (eGFR) in the controlled MS studies (Pool A), which show small increases in eGFR with BG00012 treatment compared with placebo during 2 years observational period, further suggest that BG00012 does not have a deleterious effect on renal function. While small increases in the incidence of proteinuria (with 240 mg TID dosing) and small decreases in serum 1,25-dihydroxyvitamin have also been*	It has been noted that the sponsor has made relevant statements in the EU SmPC section 5.3, but Australian clinicians usually do not refer to the EU SmPC. A similar statement should be included in the Australian PI. The EU SmPC statement is as follows: *'Kidney changes were observed after repeated oral administration of dimethyl fumarate in mice, rats, dogs, and monkeys. Renal tubule*

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	OPR evaluator's comment
	observed with BG00012, these changes have not been associated with clinically meaningful sequelae. Based on extensive analyses of safety data from clinical studies of BG00012, the sponsor considers there is no increased risk of renal or urinary events with BG00012 treatment, and proposes dosing adjustment and close monitoring of renal function are not warranted at this time.'	*epithelia regeneration, suggestive of tubule epithelial injury, was observed in all species. Renal tubular hyperplasia was observed in rats with life time dosing (2 year study). Cortical atrophy was observed in dogs and monkeys, and in monkeys single cell necrosis and interstitial fibrosis were observed in animals 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.'*
6. The combination with other fumaric acid derivatives can easily lead to a nephrotoxic dose potentially leading to renal impairment or acute renal failure even in patients without previous renal compromise. This should be reflected in the proposed Australian PI (or a statement to that effect); and	*'The proposed Australian product information informs prescribers that concurrent treatment with BG00012 and other fumaric acid derivatives (topical or systemic) should be avoided. The sponsor agrees to amend the text to indicate that concurrent use should be avoided as such clinical scenarios have not been studied.'*	This was considered acceptable.
7. Regarding overdose, the sponsor should	*'The sponsor acknowledges that when overdose occurs (i.e. a dose*	This was considered

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	OPR evaluator's comment
include the potential of renal impairment even in doses marginally higher than therapeutic doses, the expected symptoms and signs, and initial management measures (or statements to that effect).	*higher than therapeutic dose), the potential risk to renal function is unknown. No cases of overdose have been reported, so it cannot be concluded that a dose marginally higher than therapeutic dose will increase risk of renal impairment. In overdose, an exacerbation of the common side effects of flushing and gastrointestinal symptoms would be expected. Vomiting might also occur during overdose. Although vomiting could reduce the amount of DMF from overdose in the gastrointestinal system and subsequently in plasma, vomiting alone may not reliably prevent an increased plasma level from being achieved. In the event of an overdose, the sponsor recommends discontinuation of BG00012 immediately and that medical care for the evaluation and treatment should be sought.* *As directed by the TGA, a revised PI will be submitted following receipt of the final evaluation reports.'*	acceptable.
8. In regard to the proposed routine risk minimisation activities, it was recommended to the Delegate that the draft consumer medicine information (CMI) document be revised as follows: a. Patients should inform their medical practitioner of any history of kidney disease;	a. The sponsor agreed to revise the draft consumer medicine information to advise patients to inform their doctor of any history of kidney disease. Per the direction from TGA, the revised CMI will not be submitted until after the final evaluation reports are received.	This was considered acceptable.
b. Patients should inform their medical practitioner of any history of contact dermatitis or allergies to fumaric acid derivatives;	The sponsor stated that *'[f]ormulations of dimethyl fumarate for industrial use, agricultural use and medicinal use are not the same.'* *The sponsor concludes: 'Thus, based on the many differences between non-medicinal grade dimethyl fumarate and BG00012, and the absence of a signal with respect to contact dermitis or*	This was considered acceptable.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	OPR evaluator's comment
	immediate-type allergic reactions, these events are not considered appropriate to add to the RMP as an important potential risk and would not be appropriate to add to the consumer medicine information. The sponsor will continue to be vigilant for any reports of serious allergic reactions and update the RMP if appropriate.'	

It was considered that the sponsor's response to the TGA 's consolidated request for information adequately addressed all of the issues identified in the RMP evaluation report, except for two minor issues outlined below.

After the RMP evaluation report had been completed and after the sponsor's response, the sponsor submitted new information about case reports on progressive multifocal leukoencephalopathy. The information in regard to this new issue was unavailable at the Round 1 stage of the RMP evaluation.

Hence one major change to the PI is recommended by the OPR evaluator in addition to the abovementioned two issues (see below).

Additional recommendations in response to new information provided by the sponsor

On 18 February 2013, Biogen Idec provided an update to a safety communication item. The sponsor informed the TGA about the upcoming publication of two cases of progressive multifocal leukoencephalopathy (PML) while on treatment with compounded fumaric acid esters (including dimethyl fumarate). Now, a total number of four cases are known. The number of reports of PML for fumaric acid derivatives lies between the number for rituximab or natalizumab and other immunsupressants (alemtuzumab, cyclophosphamide, prednisolone, mycophenolate mofetil, tacrolimus and dexamethasone). Furthermore, lymphopaenia is an Ongoing Safety Concern for dimethyl fumarate. Given that the identified cases seem to be confounded and given that a mixture of fumaric acid esters was used, no definite link can be established. After consideration of the above, the OPR reviewer makes the following recommendations in addition to the previous recommendations:

A black box warning (as in natulizumab or rituximab) seems to be unnecessary at this stage. But a warning in the PI does seem to be indicated as a preventative measure for all immunosupressants with a higher proportion of PML cases and lymphopaenia as an Ongoing Safety Concern. The proposed Australian PI should contain a statement that four cases of PML were described in patients on treatment with fumaric acid esters (including dimethyl fumarate), even though dimethyl fumarate was not identified as the definite cause. Furthermore, the PI should include a statement that patients on immunosuppressants (including dimethyl fumarate) should be monitored for clinical features of PML, in particular those with risk factors for PML and that all necessary investigations should be undertaken if suspected (including anti-JC virus antibodies, MRI, and JC virus DNA in cerebrospinal fluid) (or a statement to that effect).

Summary of recommendations

Outstanding issues

Issues in relation to the RMP

Existing recommendations:

The sponsor should submit a protocol for their planned clinical study in patients between ages of 10 and 17 years old (as the sponsor has agreed to do).

In the proposed Australian PI, the sponsor should include statement on observed kidney changes after repeated oral administration of dimethyl fumarate in mice, rats, dogs, and monkeys.

New recommendation:

The proposed Australian PI should contain a statement that four cases of PML were described in patients on treatment with fumaric acid esters (including dimethyl fumarate), even though dimethyl fumarate was not identified as the definite cause. Furthermore, the

PI should include a statement that patients on immunosuppressants (including dimethyl fumarate) should be monitored for clinical features of PML, in particular those with risk factors for PML, and that all necessary investigations should be undertaken if suspected (including anti-JC virus antibodies, MRI, and JC virus DNA in cerebrospinal fluid) (or a statement to that effect).

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

ACSOM advice was not sought for this submission.

Comments on the safety specification of the RMP

Clinical Evaluation Report

The clinical evaluator made the following summary comment in regard to safety specifications in the draft RMP: *'Overall, the RMP seemed appropriate. BG00012 does not appear to be associated with major safety concerns and routine pharmacovigilance activities should pick up any unexpected problems. These activities will include a specific focus on the incidence and consequences of lymphopaenia.'*

OPR evaluator's comment: lymphopaenia has been adequately addressed by the sponsor in the RMP.

Nonclinical evaluation Report

Nonclinical evaluator's comment: *'Results and conclusions drawn from the nonclinical program for DMF detailed in the sponsor's draft Risk Management Plan are in general concordance with those of the Nonclinical Evaluator.'*

Suggested wording for conditions of registration

RMP

Implement EU-RMP Version 1 (dated March 2012, DLP not given) and any future updates as a condition of registration.

PSUR

Post marketing reports are to be provided annually until the period covered by such reports is not less than three years from the date of the approval letter. No fewer than three annual reports are required. The reports are to meet the requirements for Periodic Safety Update Reports (PSURs) as described in the Eudralex Volume 9 relating to PSURs. Unless agreed separately between the supplier, who is the recipient of the approval and the TGA, the first report must be submitted to the TGA no later than 15 calendar months after the date of the approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report. The annual submission may be made up of two Periodic Safety Update Reports each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available. Submission of the report must be within the 60 days of the data lock point for the report (or where applicable, the second of the two six monthly reports) as required by the Eudralex Volume 9.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There were no objections to approval from a quality/biopharmaceutics perspective. DMF was discussed by the Pharmaceutical Sub Committee (PSC) of the Advisory Committee on Prescription Medicines (ACPM) at its meeting on 25 March 2013.

The drug products are enteric coated microtablets containing dimethyl fumarate 120 mg or 240 mg. A gastro-resistant dosage form was necessary due to the acid lability of DMF. Dimethyl fumarate (DMF) is rapidly hydrolysed to the active monomethyl fumarate (MMF). Note that in the clinical dossier the sponsor referred to this metabolite as monomethyl fumarate (MMF). As the parent drug is undetectable in human blood or plasma the outcomes of all supportive bioavailability/ bioequivalence studies have been determined on the basis of methyl hydrogen fumarate concentrations.

Nonclinical

The nonclinical evaluator has supported approval of DMF provided that the clinical data are sufficient to allay concerns regarding renal toxicity and that clinical efficacy is sufficient to outweigh concerns regarding renal carcinogenicity.

The main target organs identified in toxicity studies were the nonglandular stomach (forestomach) (mouse and rat), the kidney (rat, dog and monkey), testes (mouse, rat and dog) and the liver (rat). The kidney findings were the only findings that are considered to be a risk in patients. Urinary albumin was established as a marker for DMF-induced renal toxicity in the rat, although results were confounded by DMF-induced exacerbation of rodent-specific nephropathy. Urinary albumin and β_2 microglobulin were monitored in clinical trials.

Renal tubular adenomas and carcinomas were observed in the mouse and rat carcinogenicity studies. Incidences of at least one of these tumours were significantly increased at an animal/human exposure ratio of 4 in both species, but some increases were observed at clinically relevant exposures. A mechanism of tumourigenesis related to exacerbation of rodent-specific nephropathy appears likely to make a contribution to, but not be solely responsible for, the development of these tumours. Thus, the evaluator did not consider it was appropriate to disregard these tumours as irrelevant to humans because of such a mechanism and they might pose a risk to patients.

Although there were some positive results in the chromosome aberration studies in the absence of metabolic activation a weight of evidence approach suggests a low risk of genotoxicity in patients.

Reproductive toxicity findings in the nonclinical studies were considered by the nonclinical evaluator to be most likely to be due to maternal toxicity, and therefore their clinical relevance is considered to be low. The recommended pregnancy category is B1.

DMF was shown both *in vitro* and *in vivo* to have anti-inflammatory and neuroprotective activity. The concentrations and doses showing activity in the primary pharmacology studies were similar to, or slightly higher than, those which are clinically relevant. Plasma protein binding was low in all species but particularly in rats (0%) and monkeys (3%) and was highest in humans (23-40%).

The proposed metabolic pathway was the same for all species and involves metabolism by esterases and the citric acid cycle enzymes with no involvement of CYP enzymes. In both rats and humans in addition to the major route of excretion via expired air renal excretion was also substantial and faecal excretion was minimal. There was no evidence of potential for pharmacokinetic drug interactions mediated by inhibition of CYP enzymes or P-glycoprotein, or enzyme induction.

Clinical

Pharmacology

Dimethyl fumarate is rapidly and completely converted to monomethyl fumarate (MMF), the primary active metabolite, by hydrolysis. DMF is extensively metabolised by esterases in the gastrointestinal tract and blood and tissues before it reaches the systemic circulation. DMF at normal doses is barely detectable in the blood. The PK studies assessed MMF.

No absolute bioavailability study was performed however in a radio-label study (Study 109HV102) less than 1% of radioactivity was recoverable from faeces, suggesting a high level of absorption after oral administration. The proposed formulation contains enteric-coated microtablets, specifically aimed at delaying absorption of DMF to improve tolerability.

T_{max} usually occurs in 2-2.5 h. Exposure to MMF (C_{max} and AUC) is dose proportional and there is no significant difference between single and multi-dose pharmacokinetics. The volume of distribution (Vd) is approximately 60 to 70 L, similar to that of total body water. Human plasma protein binding of DMF was shown to be in the range of 58.0% to 68.5%. However DMF rapidly hydrolyses to MMF which has a lower range of binding in pooled human plasma (unbound fractions ranged from 55.1% to 66.1%).

A normal meal did not influence the AUC or C_{max} of MMF. A fat rich meal didn't alter the AUC but reduced the C_{max} and $t_{½}$: under fasting conditions C_{max} was 50% to 60% higher and the $t_{½}$ was approximately 2 fold less than after a fatty meal. With both meal types T_{max} increased significantly. T_{max} was 2.29 h in the fasted state, compared to 4.32 h in the fed state (normal meal) and T_{max} was delayed from 1.93 h in the fasted state to 5.37 h in the fed state (fat-rich meal).

MMF is metabolised in the Krebs (citric acid) cycle in mitochondria and is largely excreted as CO_2, with a terminal half-life of about one hour. Exhalation of CO_2 accounts for 40 to 60% of a radioactive dose. The metabolism of MMF also produces citric acid and fumaric acid metabolites. Glucose has also been identified as an end metabolite suggesting that some radio-labelled carbon from DMF is processed via normal endogenous metabolic process and subsequently becomes incorporated into endogenous cellular components. Approximately 15% of a radio-labelled dose is recoverable from urine.

There is high intra- and inter-individual variability in the PK of DMF/MMF. The sponsor has hypothesised that this may be due to the complicated interplay between dissolution, absorption and pre-systemic conversion from DMF into MMF and the downstream metabolites but some evidence suggests multiple absorption/pre-systemic sites of metabolism along the GI tract. Body weight is the main covariate of exposure (C_{max} and AUC) in relapsing remitting multiple sclerosis (RRMS) subjects.

No significant PK interactions of MMF have been demonstrated in humans. Interaction studies have been performed with MMF and beta-interferon 1a (Avonex), glatiramer acetate (Copaxone), aspirin and alcohol. Neither DMF nor MMF inhibited CYP2D6 or CYP3A4 at clinically relevant concentrations. The induction potential of MMF appears to be low as is the potential for the inhibition of other CYP-isoforms (1A2, 2B6, 2C8, 2C9, 2C19, 2E1). MMF was not an inducer or inhibitor of P-gp.

The pharmacokinetics has not been assessed in adolescents, patients aged over 65 years or in patients with significant impairment of renal or hepatic function.

The precise mechanism of action of DMF in MS remains unclear but there is some evidence that it modifies activation of the nuclear factor (erythroid-derived 2)-related factor 2 (NRf2) antioxidant response pathway, which plays a role in defending cells from oxidative stress. It is not known whether other potential mechanisms such as immune modulation

play a more important role. There are no direct PK/PD data relating the concentration of MMF to the therapeutic effects of DMF in MS. DMF does not cause QT prolongation. Flushing is a common side effect but this is not clearly dose-related. The mechanism for flushing is not clear, though this was examined in 2 studies described by the clinical evaluator above.

Efficacy

Two pivotal studies (Studies 301 and 302), a supportive dose-finding study and an extension study (Study 303) provided efficacy data. The pivotal studies are comprehensively described in the CER. Both these studies were randomised, double-blind, and placebo-controlled studies in which subjects with RRMS were treated for 2 years (96 weeks).

The pivotal studies were designed to have sufficient statistical power to detect a reduction in relapses, which was the primary efficacy focus in each study, though relapses were analysed differently in the two studies. In Study 301 the primary endpoint was the proportion of patients relapsed whereas in Study 302 it was the assessed annualised relapse rate. The proportion of subjects relapsed was a secondary endpoint in Study 302. MRI assessments and disability progression assessed using the expanded disability status scale (EDSS) were secondary endpoints in both pivotal studies. DMF doses of 240 mg BID and TID were assessed in both studies. In Study 302, glatiramer 20 mg once daily via subcutaneous injection was an active comparator.

Both studies enrolled subjects aged 18 to 55 years inclusive with a confirmed diagnosis of RRMS according to McDonald criteria 1 to 4.[34] Baseline EDSS was to be between 0.0 (normal neurological examination) and 5.0 (the person is able to walk 200 meters without aid or rest; disability impairs full daily activities such as working a full day without special provisions) inclusive.

Subjects were required to have had at least 1 relapse within the 12 months prior to randomisation, with a prior brain MRI demonstrating lesion(s) consistent with MS, or evidence of Gd-enhancing lesion(s) of the brain on an MRI within the 6 weeks prior to randomisation. MS relapse within the 50 days prior to randomisation, not stabilised from a previous relapse prior to randomisation and recent treatment with most immune-modifying treatments for MS were exclusion criteria. Subjects enrolled in Study 302 were required not to have previously received glatiramer.

Across the two studies approximately half the subjects were naïve to MS therapies (52%). The mean time since diagnosis was 5.2 years with a range 0 to 33 years and the mean time since symptom onset was 8.1 years. In the 12 months prior to study entry 25% of subjects had experienced 2 relapses and 4% had 3 or more relapses. The mean number of relapses was 1.3 in the 12 months prior to study entry and 2.5 in the 3 years prior to study commencement. 15% of subjects were enrolled with a baseline EDSS of 4 to 5.

Subjects were enrolled into Studies 301 and 302 from 34 countries grouped into 3 pre-defined regions based on geography, type of health care system and access to health care. About 18% of subjects were enrolled in Region 1 (US), 30% of subjects in Region 2 (Western Europe plus other countries), and 53% of subjects in Region 3 (Eastern Europe, India, Guatemala and Mexico). Each study was performed in all 3 regions.

A total of 1234 subjects were assessed for efficacy in Study 301. During study at least one relapse was reported in 42% of subjects given placebo, 24% given DMF BID and by 23% given DMF TID. The Kaplan-Meier estimate of the proportion of subjects relapsed at 2

[34] Polman CH, Wolinsky JS, Reingold SC. Multiple sclerosis diagnostic criteria: three years later. Mult Scler. 2005;11(1):5-12.

years (96 weeks) was 27.0% in the DMF BID group, 26.0% in the TID group and 46.1% in the placebo group, a relative reduction of 41% for the BID group and 44% for the TID group. These results were statistically significant for both dose groups. In absolute terms the difference between placebo and DMF in relapse rate was in the region of 19% for either dose. This implies that five patients would need to be treated for two years for one extra patient to be relapse-free. Relative to placebo the hazard ratios were 0.51 (95% CI, 0.40, 0.66) for DMF BID and 0.50 (95%CI, 0.39, 0.65) for DMF TID, indicating an instantaneous risk of relapse was the reduced by 49% ($p<0.0001$) and 50% ($p< 0.001$) with DMF BID and TID respectively.

In Study 301 the estimated proportion of subjects showing sustained progression (for ≥12 weeks) after 2 years was 27.1% for subjects given placebo compared with 16.4% for DMF BID and 17.7% for DMF TID, relative reductions of 39% and 35% respectively. These reductions were statistically significant for both DMF doses. Differences between either dose of DMF and placebo were not statistically significant for the 24 week confirmed progression in disability. MRI endpoints also favoured active treatment in the cohort of patients where this endpoint was available.

Tables 22-24 in the CER show MRI results (Attachment 2). The mean number of new or newly enlarging T2 hyperintense lesions was 2.6 for subjects given DMF BID, 4.4 for subjects given DMF TID and 17.0 for subjects given placebo. The percentage reductions were 85% and 74% respectively. Statistical comparisons with placebo for this parameter were highly significant ($p<0.0001$ for either dose group vs. placebo). Similarly favourable results were obtained for Gd-enhancing lesions. T1 hypointense lesions are thought to correlate with loss of axons in a plaque and hence with permanent loss of functional white matter and ultimately with cumulative disability. T1 hypointense lesions were reduced with active treatment from an adjusted mean of 5.6 in the placebo group to 1.5 and 2.1 in the 240mg BID and 240mg TID groups respectively ($p<0.0001$ for either dose group vs. placebo).

A total of 1417 subjects were assessed for efficacy in Study 302. During study at least one relapse was reported in 39% of subjects given placebo, 26% given DMF BID, 22% given DMF TID and 30% given glatiramer. The adjusted annualised relapse rate at 2 years for the ITT population was 40.1% for placebo, 22.4% for DMF BID, 20% for DMF TID and 28.6% for glatiramer. The percentage reduction relative to placebo in the adjusted annualised relapse was 44% for DMF BID and 51% for DMF TID respectively. All 3 active treatment arms were statistically superior to placebo for reduction in annualised relapse rate.

In Study 302, the number of new or newly enlarging T2 hyperintense lesions was significantly reduced relative to placebo by DMF at either dose. The mean number of lesions was 19.9 in the placebo group (adjusted 17.4) compared with 5.7 and 5.1 in the BID and TID groups respectively (adjusted 5.1 and 4.7), an adjusted reduction of 71% and 73% respectively. The glatiramer group showed an intermediate benefit with a mean of 9.6 lesions (adjusted 8.0, a 54% reduction relative to placebo). All three active treatments were statistically superior to placebo ($p<0.0001$). The higher TID dose of DMF was narrowly superior to glatiramer according to the 95% CIs of the adjusted means but the proposed BID dose showed overlapping results with glatiramer. The results for T1 hypointense lesions ("black holes") were also highly favourable with both DMF dose groups showing clear superiority over placebo and glatiramer showing a significant result.

In Study 302 the proportion of patients showing EDSS progression sustained for 12 weeks was 16.9% for placebo, 15.6% for glatiramer, 13.0% for DMF TID and 12.8% for DMF BID. None of the active treatments were statistically significantly different from placebo for disability progression.

A combined efficacy analysis was also performed which generally confirmed the outcomes of the individual studies. Efficacy results from the combined analysis are shown in the CER. The pooled analysis of proportion of subjects with progression of disability was useful because this endpoint had been positive in Study 301 but negative in Study 302. In the combined analysis the 12 week confirmed disability progression at 2 years, measured by increase in EDSS (ITT population) was 22.2% for placebo, 15.5% for DMF TID (p=0.0059) and 14.6% for DMF BID (p=0.0034). Hazard ratios for the active versus placebo comparisons were also statistically significant.

The 24 week confirmed disability progression was performed as a prespecified sensitivity analysis. There was a trend towards active treatment having less confirmed 24 week confirmed progression but statistical significance was not reached in either study. Statistical significance for this endpoint was demonstrated in the combined analysis. For the combined analysis the estimated proportion with 24 week confirmed disability progression was 14.8% for placebo, 10.5% for DMF BID(p= 0.0278) and 10.4%(p= 0.0177) for DMF TID. A summary of time to confirmed progression of disability at 2 years for both the 12 week and 24 week confirmation is shown in Figure 5 in of the CER (Attachment 2).

Safety

A total of 2560 subjects with MS have been exposed to DMF, accounting for approximately 3600 person-years of exposure with 1469 subjects having had exposure of 1 year or longer and 1095 with 2 years or longer exposure at or above the proposed dose. Additional safety data from pharmacology studies performed in healthy subjects and other efficacy/ safety studies in subjects with rheumatoid arthritis and psoriasis were also available.

Safety data from the dose-ranging study (Study C-1900) and the two pivotal studies were pooled (Pool A). This pool comprised 2907 patients (1720 given DMF, 836 given placebo and 351 given glatiramer. These were placebo-controlled studies. Data from the uncontrolled extension phase of Study C-1900 and the uncontrolled Phase III extension study (Study 303) were combined with Pool A studies as Pool B. That pool included 2468 unique subjects treated with DMF.

There were 7 deaths reported during the study period but none were considered related to treatment with DMF. Five occurred in Studies 301 and 302, these were: ischemic stroke in a placebo-treated subject; traumatic brain injury from a bicycle accident in a subject given DMF BID; an MVA in a subject receiving DMF TID; complications of an MS relapse in a subject given DMF TID and suicide in a subject given glatiramer. The 2 other deaths were in Study 303: one due to MS relapse with cardiopulmonary arrest related to paraplegia and respiratory muscle weakness in a subject given DMF BID and the other was due to suicide by paracetamol overdose in a subject given DMF TID.

In Pool A discontinuations due to AEs were slightly more common with DMF than placebo (11% placebo versus 14% DMF BID, 14% DMF TID, 10% glatiramer). The most common AE leading to discontinuation was MS relapse, which was reported more frequently with placebo than with DMF (placebo 6% versus 1% DMF BID, 2% DMF TID, 2% glatiramer). In the DMF groups there was an increased incidence of discontinuations due to gastrointestinal AE with <1% placebo versus 4% DMF BID, 6% DMF TID, <1% glatiramer). This difference was largely accounted for by an increased incidence in diarrhoea, nausea, vomiting and abdominal pain.

The incidence of treatment discontinuation due to flushing was also higher in the DMF groups than in the placebo group (<1% placebo versus 3% DMF BID, 2% DMF TID, 0% glatiramer). Discontinuation due to skin disorders was more common with DMF (<1% placebo versus 2% DMF BID, 2% DMF TID, <1% glatiramer). Treatment discontinuation due to elevations in liver transaminases was low and balanced across groups (<1% for

each of alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, hepatic enzyme increased).

In Pool A, AEs reported at an increased incidence (≥2%) in subjects treated with DMF BID compared to placebo were: flushing and hot flush; GI events (for example, diarrhoea, nausea, abdominal pain upper, abdominal pain, vomiting, and dyspepsia); skin events (pruritus, rash, and erythema); nasopharyngitis; urinary tract infection; upper respiratory tract infection; albumin urine present; proteinuria; microalbuminuria; and AST increased. These incidences were not dose-related.

AEs reported in the total DMF experience for MS subjects (Pool B) were very similar to those reported in the controlled MS studies. The most common events (≥10%) in subjects given DMF were flushing and GI events (diarrhoea, nausea, abdominal pain and upper abdominal pain). About 30% of subjects in Pool A given DMF reported flushing as an AE. The incidence of flushing reduced during continued treatment but it is unclear whether this represents a true reduction in flushing or a failure of patients and clinicians to re-report a persistent side effect.

Only a small proportion of patients had AST or ALT values ≥ 3 times the upper limit of normal (ULN) and the proportion of such patients was similar across groups. There were no cases of DMF-treated subjects who had concurrent elevations of hepatic transaminases ≥3 times ULN and an elevated total bilirubin >2 × ULN. SAEs involving hepatic enzymes were rare. In Pool A, 2 placebo recipients reported SAEs of "hepatic enzymes increased" and 1 subject in the DMF BID group had an SAE of cholestatic hepatitis.

DMF treatment was associated with a reduction in mean white blood cell (WBC) and lymphocyte counts during the first year by approximately 10% and 30%, respectively followed by a plateau. Mean and median WBC and lymphocyte counts remained within normal limits. WBC counts $<3.0 \times 10^9$/L and lymphocyte counts $<0.5 \times 10^9$/L were reported in 6 to 7% of subjects given DMF. These low counts were not associated with serious infections. No cases of leukopaenia were rated as Grade 4, but one case of lymphopaenia reached values in the Grade 4 range: a 39 year old female who received DMF 240 mg BID had normal lymphocyte counts at baseline (1.41×10^9/L) but steadily declined following Week 24. Prolonged treatment did not appear to worsen mean WBC and lymphocyte counts, which remained stable in subjects who received DMF for more than 2 years.

DMF was not associated with cardiac toxicity.

Nonclinical data suggested a possible increased risk of nephropathy and renal carcinoma for humans given DMF. Urinary albumin was established as a marker for DMF-induced renal toxicity in the rat although results were confounded by DMF-induced exacerbation of rodent-specific nephropathy. In the placebo controlled trials in MS urinalysis did not show any notable differences between groups. Albumin in the urine was reported as an AE in 6% of subjects who received DMF 240mg BID and 4% of placebo recipients. There was no substantial difference across groups in the incidence of abnormal urea, creatinine or electrolytes. There was a slightly increased incidence of shifts to high bicarbonate with DMF treatment: DMF BID (16%), DMF TID (15%), placebo (9%) and Gadolinium (10%). This is unlikely to be clinically significant.

There were no cases of Progressive Multifocal Leukoencephalopathy (PML) reported in the clinical development program however there have been 4 cases associated with the use of fumarate compounds for the treatment of psoriasis. In 3 cases of PML patients received Fumaderm®, an oral fumarate combination product belonging to the same pharmacologic class as DMF. Fumaderm contains DMF in combination with 3 monoethyl fumarate salts, which are pharmacodynamically active. Fumaderm has been licensed in Germany since 1994 for the treatment of moderate and severe forms of plaque psoriasis and postmarketing exposure is estimated to be over 150,000 patients. The cases were:

- PML diagnosed in a 57 year old woman one month after starting Fumaderm therapy. She had longstanding underlying sarcoidosis treated with steroids and methotrexate. Sarcoidosis is known to be associated with increased risk of PML.
- A 66 year old man diagnosed with PML after three years treatment with Fumaderm. Significant risk factors included prior treatment with efalizumab, which is known to increase the risk of PML, prior melanoma developing during efalizumab treatment, and decreased immunoglobulins of unclear etiology.
- A 74 year old man developed PML after three years treatment with Fumaderm. Prior treatment for psoriasis included acitretine and methotrexate. This patient continued therapy with Fumaderm despite values of lymphocytes persistently under 500 for over two years.
- In the fourth case the patient had taken compounded fumarate containing DMF and copper monofumarate for 6 to 7 years and was diagnosed with PML in November 2012. This patient had no history of immunosuppressant therapies (other than the fumarate compound) and developed severe lymphopenia while on treatment.

In summary the sponsor considered there was one case of PML without clear risk factors in 159,000 person-years of Fumaderm exposure and that this is consistent with the expected background rate for this event, based on the published incidence of PML in patients with autoimmune diseases.

Risk management plan

This product was not presented to ACSOM. The RMP evaluator made recommendations for amendments to the PI.

Given the renal effects of DMF in nonclinical studies the sponsor was requested to amend the PI to advise readers of a risk of renal dysfunction and suggest monitoring. The sponsor responded noting that there has been no increased incidence of renal or urinary events observed with DMF-treated patients. This is consistent with data from Studies 301 and 302 indicating the absence of a treatment effect on β2-microglobulin (a sensitive urinary biomarker for tubular dysfunction) over 3.5 years of dosing. Additional analyses of the estimated glomerular filtration rate (eGFR) in the controlled MS studies (Pool A), which show small increases in eGFR with DMF treatment compared with placebo during 2 years observational period, further suggest that DMF does not have a deleterious effect on renal function. While small increases in the incidence of proteinuria (with 240 mg TID dosing) and small decreases in serum 1,25-dihydroxyvitamin have also been observed with DMF these changes have not been associated with clinically meaningful sequelae. Based on their analyses of safety data from clinical studies of DMF the sponsor considers there is no increased risk of renal or urinary events with DMF treatment and proposes dosing adjustment and close monitoring of renal function are not warranted at this time.

The RMP evaluator considered the new safety data concerning PML and recommended inclusion of a warning statement in the PI for all immunosupressants with a higher proportion of PML cases and lymphopaenia as an Ongoing Safety Concern. The evaluator also recommended that the proposed Australian PI should contain a statement that four cases of PML were described in patients on treatment with fumaric acid esters (including dimethyl fumarate) even though dimethyl fumarate was not identified as the definite cause. Furthermore the PI should include a statement that patients on immunosuppressants (including dimethyl fumarate) should be monitored for clinical features of PML, particularly patients with risk factors for PML and that all necessary investigations should be undertaken if PML is suspected (including anti-JC virus antibodies, MRI, and JC virus DNA in cerebrospinal fluid) (or a statement to that effect).

Risk-benefit analysis

Delegate considerations

This is an orally administered product for MS. The proposed dose regimen has been satisfactorily justified by the results of the clinical trials. The efficacy demonstrated by DMF supports claims for both a reduction in the frequency of relapses and in the progression of disability in patients with RRMS. The inclusion of an active control in one of the pivotal studies was very useful in suggesting relative efficacy of this product though there were no formal statistical comparisons between glatiramer and DMF.

There was no signal for an increase in serious infections during the clinical trial program and all Progressive Multifocal Leukoencephalopathy (PML) cases to date have had other factors which could have affected the development of PML. At this stage the Delegate was not inclined to draw specific attention to the possible development of PML for this product as was recommended by the RMP evaluator. However, the Delegate considered that (PML) should be included in the list of possible safety concerns in the Safety Specification.

The indication should be as far as possible similar to that of other products tested in the RRMS population where a reduction in relapse rate and disability progression compared with placebo has been demonstrated.

Questions for the ACPM

The general advice of the committee on the quality, safety and efficacy of dimethyl fumarate (Tecfidera) for the proposed indication of *Tecfidera is indicated in patients with relapsing forms multiple sclerosis to reduce the frequency of relapses and to delay the progression of disability* is requested. In addition the committee was requested to provide advice on the following specific issues:

1. The proposed indication will include patients with secondary progressive MS who still have relapses. Given the pivotal clinical trial population was restricted to those with RRMS is it reasonable to include patients with MS who have some permanent disability in addition to relapses in the indications for DMF?
2. The sponsor has not proposed a monitoring regimen for lymphopenia, though lymphocyte counts <0.5x109/L were observed in 6% of patients treated with dimethyl fumarate. The Committee was asked to consider whether routine haematological monitoring of patients should be recommended, and if so how frequently and what action should be taken should severe lymphopenia develop.
3. A significantly increased incidence of serious or severe infections was not seen in the pivotal clinical trials though dimethyl fumarate is associated with a significant incidence of lymphopenia. Does the Committee consider specific statements advising of the possibility of serious or severe infection in patients taking dimethyl fumarate is warranted?
4. It is not known if long term use of DMF will be associated with an increased incidence of nephropathy and/or renal adenocarcinoma as was seen in nonclinical studies. Does the Committee consider the sponsor should be required to specifically monitor and report the incidence of nephropathy and renal adenocarcinoma in patients taking DMF?
5. The RMP evaluator has recommended inclusion of a warning statement in the PI for all immunosupressants with a higher proportion of PML cases and lymphopaenia as an ongoing safety concern and has proposed a statement as discussed in the RMP sub-section of this document. Does the Committee consider the current evidence warrants such a statement?

6. The sponsor has included a statement that reducing the dose to 120 mg BID for 1 month may reduce the incidence of flushing and gastrointestinal side effects. The Committee was asked to consider whether this statement should be permitted in the absence of information on the effect of the dose reduction on efficacy or on side effects.

Response from sponsor

Indication recommendation

Biogen Idec acknowledged the Delegate's comments on the revised wording of the Indications Section of the Product Information and had no further comments to make on the clinical evaluation. Per the Delegate's request, Biogen Idec has amended the indication statement to

"Tecfidera is indicated in patients with relapsing forms of Multiple Sclerosis to reduce the frequency of relapses and to delay the progression of disability."

Quality/pharmaceutical chemistry evaluation

Biogen Idec acknowledged the Delegate's summary of the Quality evaluation and had no further comments to make.

Nonclinical evaluation

Biogen Idec acknowledged the Delegate's summary of the nonclinical evaluation.

For the proposed changes to the Product Information, Biogen Idec supplied TGA with proposed revisions to address the recommendations of the nonclinical evaluator.

The sponsor modified the PI to incorporate the recommendations made by the nonclinical evaluator with the exception of the following:

For consistency and flow of the PI, minor modifications have been incorporated in the *Effects on Fertility, Use in Pregnancy, Genotoxicity* and *Carcinogenicity* under *Precautions* sections.

In response to the evaluator's pharmacodynamics recommendation to include the statement in the PI, "…*although the magnitude of up-regulation observed in tissues of the central nervous system was small*" the sponsor agreed that in our submission, the absolute levels of mRNA changes do not appear to be as robust in the brain as in peripheral tissues. Subsequent studies have identified more appropriate CNS specific gene targets of Nrf2, and these are more dynamically regulated (up to 6 fold over baseline in certain brain regions). It should also be noted that although the exact mechanism of protective effects downstream from Nrf2 activation in the brain is unclear, regardless of the mechanism or degree of gene induction, the beneficial effects of dimethyl fumarate (DMF) treatment have been observed in multiple models of neurotoxicity. This suggests that even the modest changes observed for some Nrf2 target genes may be sufficient to confer protection against toxic stress. Thus, the evaluator's comments regarding low gene activation may be taken out of context to suggest DMF has a low, if any, effect in the CNS, however current data suggests otherwise and the sponsor respectfully requested that this statement not be included in the PI.

The immunomodulatory effects of oral DMF treatment *in vivo* has been demonstrated in psoriasis patients receiving the same formulation of DMF used in the multiple sclerosis clinical program. As noted by the nonclinical evaluator, in studies conducted by Ghoreschi et al. (2011)[35], the authors demonstrate a clear effect of biasing expression of T-helper cells from a pro-inflammatory Th1/17 phenotype to an anti-inflammatory Th2 phenotype.

[35] Ghoreschi K, Brück J, Kellerer C, et al. Fumarates improve psoriasis and multiple sclerosis by inducing type II dendritic cells. J Exp Med. 2011;208(11):2291-303.

Biogen Idec clarified that the information and publication was referenced in the sponsor's Pharmacology Written Summary, though a copy of the reference itself was not provided in the submission. Therefore, the sponsor respectfully requested that the text '*and moreover affects lymphocyte phenotypes through a down-regulation of pro-inflammatory cytokine profiles (TH1, TH17), and biases towards anti-inflammatory production (TH2)*' be retained in the PI.

Clinical evaluation

Biogen Idec acknowledged the Delegate's summary of the clinical evaluation and has the following comments:

Clinical efficacy

The sponsor acknowledged the Delegate's and clinical evaluator's summary of clinical efficacy and was encouraged by the positive benefit/risk assessment in the Delegate's overview.

Relative risk reduction:

The sponsor carefully considered the Delegate's recommendation and noted that this request was different from the clinical evaluator's final comment dated 18 February, 2013, and interpreted this request as referring to the clinical evaluator's final comments.

The sponsor agreed with the clinical evaluator's comments that it is important to provide clear and meaningful expression of treatment effects in the PI, and accordingly made changes to the proposed PI:

- The % reduction labelled as "relative reductions" which were considered potentially ambiguous by the clinical evaluator has been removed and replaced them with the hazard ratios themselves and the associated 95% confidence intervals (CI), for proportion relapsed and progression, and have clearly labeled them.

The hazard ratios and 95% CI statistics are consistent with the most recently approved TGA product label for oral MS products (Gilenya and Aubagio), in which only hazard ratio and 95% CI for proportion/probability of subjects progressed are presented. In addition, it is consistent with how MS Phase III trials report these endpoints in publications.

However, the sponsor opted not to add the relative reduction based on the estimated proportion of subjects relapsed and proportion with disability progression (referred to also as cumulative risk reduction in the clinical evaluation comments) to the table and text in the PI, because, although these are also meaningful ways of expressing treatment effects, these statistics were not pre-specified in our statistical analysis plan, and have not been adjusted for important baseline covariates as the hazard ratios statistics have.

The sponsor believed that the changes they proposed will eliminate any potential confusion, and will allow physicians and patients to make important, informed decisions when they try to compare the efficacy across different treatment, since comparable statistics are used to express efficacy in the same set of endpoints in the PI as other oral MS treatments.

Dosing and administration

The sponsor acknowledged the request to remove the statement, *"temporary dose reduction to 120 mg twice a day may reduce the occurrence of flushing and gastrointestinal (GI) side effects. Within 1 month, the recommended dose of 240 mg twice a day orally should be resumed"* from the label. Biogen believes the statement can be supported by further analyses conducted on the existing dataset in response to other Regulatory Agencies who subsequently opted to include this language in the label. The analyses are briefly summarised below.

The protocol for trials 301 and 302 allowed for patients to reduce their dose for up to 1 month to alleviate adverse events of flushing and GI disturbances. The incidence of dose reductions or dose interruption in BG00012-treated subjects due to flushing or GI tolerability was low and a majority resumed normal dosage. In the controlled MS studies, 9% of subjects in placebo, 45% of BG00012 BID and 42% of BG00012 TID treated subjects reported flushing or other related symptoms, however only <1% of placebo and 4% of BG00012 BID and TID groups required dose reduction or dose interruption due to flushing or related symptoms.

Among those subjects who required dose reduction or dose interruption, 100% of the placebo, 71% of the BG00012 BID, and 68% of the BG00012 TID subjects resumed normal dosage. After resuming the normal dosage, approximately half of the subjects in the BG00012 BID and TID group did not experience a recurrence of flushing or related symptoms.

Similar results were seen for events of GI tolerability. Thirty-one percent of subjects in the placebo group, 40% in BG00012 BID and 43% in BG00012 TID treated subjects reported GI tolerability AEs and only 3%, 8%, and 9% of subjects in placebo, BG00012 BID and TID groups, respectively, required dose reduction or dose interruption. Among the subjects who had dose reduction or discontinuation of the BG00012 due to GI AE, 82% of placebo, 82% of BG00012 BID and 72% of the TID subjects resumed normal dosage. After resumption of the normal dosage, approximately half of the subjects in all 3 groups did not experience a recurrence of GI intolerability adverse events. Furthermore, clinical efficacy results were similar in subjects who had a dose reduction or interruption for at least one month and those who did not have a dose reduction or interruption for at least one month.

Biogen asked the TGA to consider that dosing reduction or interruption may mitigate the recurrence of flushing or GI tolerability AEs in a considerable proportion of patients and for this reason the sponsor maintained that it is appropriate to provide patients and physicians with the opportunity to reduce BG00012 dosing. In the event that the TGA did not concur with this view, Biogen was willing to consider removing the statement from the label and would be happy to discuss this further with the Delegate post ACPM.

Risk Management Plan (RMP) evaluation

Opportunistic infections

In the Tecfidera clinical program, there has been no evidence of an increased risk of serious infections. There have been no opportunistic infections in Tecfidera treated patients and no reports of PML. Biogen Idec acknowledged that decreases in lymphocyte counts have been observed with Tecfidera. Although such decreases may be associated with a theoretical risk of increased infections, no such increase was observed in the clinical trials of Tecfidera.

Biogen supports the Delegate's evaluation and recommendation,

'There was no signal for an increase in serious infections during the clinical trial program and all Progressive Multifocal Leukoencephalopathy (PML) cases to date have had other factors which could have affected the development of PML. At this stage the Delegate was not inclined to draw specific attention to the possible development of PML for this product as was recommended by the RMP evaluator. However, the Delegate considered that (PML) should be included in the list of possible safety concerns in the safety specification'.

The updated version of RMP includes a description of PML cases reported with other fumarates under the important potential risk of Serious and Opportunistic Infections. It also contains explicit commitment on the part of Biogen Idec to ensure that:

- PSURs will be submitted to TGA as per the standard conditions of registration.
- Opportunistic infections, including PML will be classified as serious

- If signaling activities indicate occurrence of increased risk of serious and opportunistic infections, TGA will be informed.
- Interim analyses for the ongoing open label observational study (109MS303) will be made after 1000 patients have completed 6 months of follow up to allow sufficient data for meaningful evaluation, then interim analyses will be conducted annually.

To include a statement regarding PML in isolation in the PI for this product unduly highlights this particular opportunistic infection that has not been seen in the clinical trials for Tecfidera. The sponsor believed that it was more appropriate to include monitoring for lymphocyte levels in the PI, as this may be considered a risk factor for any serious opportunistic infection.

Therefore the sponsor submit that it is more appropriate that the PI include a statement on lymphocyte monitoring that is based on extensive evaluation of the data. The suggested text for the PI is shown below and is followed by a summary of the supporting analyses:

> *"Tecfidera may decrease lymphocyte counts. Prior to initiating treatment with Tecfidera, a recent complete blood count (CBC) (i.e. within 6 months) is recommended. A CBC is recommended annually, and as clinically indicated. Withholding treatment should be considered in patients with serious infections until the infection(s) resolved. Tecfidera has not been studied in patients with pre-existing low lymphocyte counts and caution should be exercised when treating these patients"*

In order to define the periodicity of lymphocyte monitoring in patients treated with BG00012, the sponsor carefully examined the totality of lymphocyte count data collected in the Phase II and III MS clinical studies (Pool A). Key considerations in this evaluation consisted of the overall pattern over time of the incidence of lymphocyte values <0.5 x 109/ L, the time to first lymphocyte count <0.5 x 109/ L and the persistence of low values. Of note, approximately 50% of subjects with lymphocyte counts <0.5 x 109/L had only single value <0.5 x 109/L.

Additional analyses of lymphocyte counts <0.5 x 109/L in Pool A during the first 12 weeks revealed an incidence that was low and similar across treatment groups (Placebo: 2 subjects, <1%; BID: 2 subjects, < 1%; TID: 1 subject, <1%; and GA: 1 subject, <1%). This directly suggests that monitoring at Month 3 is not warranted.

Furthermore, prior to the Month 6 visit window (at or before Day 126), the incidence of subjects who had a lymphocyte count <0.5 x 109/ L was also low and similar across treatment groups (Placebo: 3 subjects, <1%; BID: 5 subjects, < 1%; TID: 3 subjects, <1%; and GA: 1 subject, <1%).

The incidence of BG00012-treated subjects with a first lymphocyte count <0.5 x 109/L at the Month 6 visit window and later (after Day 126) was increased relative to placebo (Placebo: 1 subjects, <1%; BID: 38 subjects, 5%; TID: 21 subject, 3%; and GA: 0 subjects), with the incidence at individual time points remaining relatively stable over time from the Month 6 to Month 24 visits. Of significant consideration, the greatest difference in the incidence of subjects who had lymphocyte counts <0.5 x 109/L in BG00012 compared to placebo was most apparent at time points starting at one year and later.

Given the information presented above, early lymphocyte monitoring prior to Month 6 (for example at month 3) is not clinically indicated as the difference from placebo only begins to emerge at time points beginning at Month 6 and are most apparent after 1 year. Furthermore, sustained low lymphocyte counts would likely be detected with the periodicity of testing presented.

Renal monitoring

Biogen Idec acknowledged the Delegate's question to the ACPM about long term renal outcomes and agreed that these should be further evaluated. Both topics have been

included within the RMP as important potential risks (renal tubular injury and malignancy) and the pharmacovigilance plan defines how these potential risks will be monitored and reported from the following sources:

- A large observational study following 5000 patients for 5 years
- Targeted follow-up of all malignancy reports and all serious renal AEs
- Evaluation of long term renal safety outcomes in the extension study, 109MS303
- Inclusion of renal safety and malignancy topics within the PSUR.

There is no evidence of an increased risk of clinically meaningful renal complications associated with Tecfidera use from the extensive renal laboratory data collected during the clinical development program. Furthermore, additional long term laboratory data is being collected from the safety extension study. For these reasons Biogen Idec did not currently recommend routine renal monitoring during the administration of Tecfidera. Although some regulatory agencies have reviewed these data and requested routine monitoring, others have supported our evidence based recommendations.

Should data from the extension study or any other source support the need for additional monitoring this will be communicated/implemented as required via post approval safety related updates to the PI.

Product Information

1. Biogen included recommendations from the nonclinical evaluation report with the exception of those noted above.
2. Biogen removed the pharmacokinetic study numbers from the PI.
3. Clinical Trials: Biogen amended the efficacy tables as described above.
4. Biogen Idec agreed to the amended indication statement.

Proposed indication:

"Tecfidera is indicated in patients with relapsing forms of Multiple Sclerosis to reduce the frequency of relapses and to delay the progression of disability."

Biogen also made amendments to the *Precaution* and *Dosing and Administration* sections of the PI.

Advisory Committee Considerations

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered these products to have an overall positive benefit–risk profile for the amended indication**;**

> *Tecfidera is indicated in patients with relapsing multiple sclerosis to reduce the frequency of relapses and to delay the progression of disability*

Proposed PI/CMI amendments:

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and specifically advised on the inclusion of the following:

- The inclusion of provisions for monitoring haematological and renal functions.
- A statement in the *Precautions* section of the PI and relevant sections of the CMI accurately reflect the possibility of serious or severe infection as a recognised risk of lymphopenia.

- A statement in the *Clinical Trials and Precautions* sections of the PI and relevant sections of the CMI to the renal effects of DMF in nonclinical studies and the proteinuria observed in the pivotal studies,
- Reference should be made to the renal effects of DMF in nonclinical studies; to the proteinuria/microalbuminuria observed in the pivotal studies and that an annual assessment of renal function and proteinuria should be considered.
- Reference should be made to PML cases associated with the use of fumarate compounds in other indications.[36]
- A statement in the *Dosage and Administration* section of the PI and relevant sections of the CMI to the possibility of temporary dose reduction for the alleviation of adverse events.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Tecfidera (dimethyl fumerate) 120 mg and 240 mg modified release tablets in blister packs for oral administration, indicated for:

> *Tecfidera is indicated in patients with relapsing multiple sclerosis to reduce the frequency of relapses and to delay the progression of disability.*

Specific conditions of registration applying to these therapeutic goods

1. The implementation in Australia of the dimethyl fumerate EU-RMP Version 1 (dated March 2012, DLP not given) and any future updates, including the submission PM-2012-00808-3-1, and any subsequent revisions, as agreed with the TGA and its Office of Product Review.

Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Attachment 2. Extract from the Clinical Evaluation Report

[36]Sponsor comment: "After the ACPM recommendations were received, further discussions were entered into with the Delegate during which it was agreed with TGA that it was not appropriate at this time to include wording relating specifically to PML in the PI. Biogen Idec and the Delegate agreed that this should be monitored on an ongoing basis as part of risk management activities but as there was no signal for increase in serious infections in the clinical program, it was not appropriate to draw specific attention to the possible development of PML for this product."

Therapeutic Goods Administration

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