16 September 2021
EMA/CHMP/555028/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Vumerity

International non-proprietary name: diroximel fumarate

Procedure No. EMEA/H/C/005437/0000

Note

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

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List of abbreviations

301	Study 109MS301 (DEFINE)
302	Study 109MS302 (CONFIRM)
303	Study 109MS303 (ENDORSE)
A301	Study ALKS 8700-A301 (EVOLVE-MS-1)
A302	Study ALKS 8700-A302 (EVOLVE-MS-2)
ADME	Absorption, Distribution, Metabolism and Elimination
ADR	Adverse Drug Reactions
AESIs	Adverse Event of Special Interest
AEs	Adverse Effects
Akr1b8	Aldo-keto reductase family 1 member B8
ALC	Absolute Lymphocyte Count
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of covariance
ARR	Annualised Relapse Rate
AST	Aspartate Aminotransferase
AUC_{last}	Area under the plasma concentration-time curve from time zero to time of last measurable concentration
BID	*Bis In Die;* twice a day
BMI	Body Mass Index
CIs	Confidence Intervals
C_{max}	Maximum Observed Concentration
CNS	Central Nervous System
CPN	Chronic Progressive Nephropathy
C-SSRS	Columbia-Suicide Severity Rating Scale
DB	Double Blind
DDIs	Drug-Drug Interactions
DILI	Drug-Induced Liver Injury
DMF	Dimethyl Fumarate
DMTs	Disease Modifying Treatments
DR	Delayed release
DRF	Diroximel fumarate
EAE	Experimental Autoimmune Encephalomyelitis
ECG	Electrocardiogram
EDSS	Expanded Disability Status Scale

EQ-5D-5L	EuroQoL Group Health Outcome Measure 5-Level
FAS	Full Analysis Set
FT-IR	Fourier Transform Infrared Spectroscopy
FSQ	Flushing Symptom Questionnaire
GA	Glatiramer Acetate
GdE	Gadolinium-Enhancing
GFSS	Global Flushing Severity Score
GGT	Gamma-Glutamyltransferase
GI	Gastrointestinal
GGISIS	Global GI Symptom and Impact Scale
GLP	Good Laboratory Practice
hERG	human Ether-à-go-go Related Gene
HES	2 HydroxyEthyl Succinimide
HDL	High-Density Lipoprotein
HDPE	High Density Polyethylene
HO1	Haem oxygenase 1
HPLC	High performance liquid chromatography
HPMC	Hydroxypropyl Methylcellulose
HS-GC	Headspace-gas chromatography
IBC	Intermediate bulk container
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-MS	Inductively coupled plasma mass spectrometry
IGISIS	Individual GI Symptom and Impact Scale
LFT	Liver Function Tests
LDH	Lactate dehydrogenase
LDL	Low-Density Lipoprotein
LLN	Lower Limit of Normal
MAA	Marketing Authorisation Application
MAGISS	Modified Acute Gastrointestinal Symptom Scale
MMF	Monomethyl Fumarate
MS	Multiple Sclerosis
MO	Major Objection
MOGISS	Modified Overall Gastrointestinal Symptom Scale
MRHD	Maximum Recommended Human Dose
MRI	Magnetic Resonance Imaging

NEDA	No Evidence of Disease Activity
NOAELs	No-Observed-Adverse-Effect Levels
Nrf2	Nuclear factor erythroid 2-related factor 2
OL	Open Label
OLE	Open Label Extension
Osgin1	Oxidative stress induced growth inhibitor 1
PBVC	Percent Brain Volume Change
PCS	Potentially Clinically Significant
PD	Pharmacodynamic
PDE	Permitted daily dose
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic
PML	Progressive Multifocal Leukoencephalopathy
PND	Post-Natal Day
popPK	Population PK
PPQ	Process performance qualification
PRO	Patient Reported Outcomes
PTs	Preferred Terms
PXRD	Powder X-Ray Diffraction
RMM	Risk Minimisation Measures
RMS	Relapsing Multiple Sclerosis
RRMS	Relapsing-Remitting Multiple Sclerosis
SAEs	Serious Adverse Events
SAP	Statistical Analysis Plan
SD	Standard Deviation
SF-12	12-item Short-Form health survey
SOC	System Organ Class
TCA	Tricarboxylic Acid
TEAEs	Treatment-Emergent Adverse Events
t_{max}	Time of Maximum concentration observed
$t_{1/2}$	Half life
T25-FW	Timed 25-foot walk
ULN	Upper Limit Normal
UV	Ultraviolet
WBC	White Blood Cell

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Biogen Netherlands B.V. submitted on 16 November 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Vumerity, through the centralised procedure under Article 3 (2) (b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 19 September 2019. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on the potential of a significant therapeutic innovation.

The applicant applied for the following indication:

> Vumerity is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (see section 5.1 for important information on the populations for which efficacy has been established).

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, quality, non-clinical and clinical data with a letter from the MAH Biogen Netherlands B.V. allowing the cross reference to relevant quality, non-clinical and/or clinical data.

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0381/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0381/2020 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

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

1.5. Scientific advice

The applicant did not seek Scientific advice from the CHMP.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Martina Weise Co-Rapporteur: Ewa Balkowiec Iskra

The Rapporteur appointed by the PRAC was:

PRAC Rapporteur: Martin Huber

The application was received by the EMA on	16 November 2020
The procedure started on	24 December 2020
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	15 March 2021
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	15 March 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	26 March 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	22 April 2021
The applicant submitted the responses to the CHMP consolidated List of Questions on	20 May 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	28 June 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	08 July 2021
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	22 July 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	13 August 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	01 September 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Vumerity on	16 September 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Multiple sclerosis (MS) is a chronic autoimmune and neurodegenerative disease of the central nervous system (CNS) characterised by inflammation, demyelination, neuronal and oligodendrocyte loss, and disruption of the blood-brain barrier, leading to irreversible deficits in physical function and cognition and an impaired quality of life. Typically, MS starts in the second or third decade of life.

Relapsing-remitting MS (RRMS) is the most common form of MS, representing approximately 85% of patients at diagnosis, and it is characterised by alternating exacerbations of neurological dysfunction followed by periods of remission with partial or total recovery and clinical stability, which can last for months or years (EMA MS guideline, EMA/CHMP/771815/2011, Rev. 2).

With the present application, the applicant seeks approval of diroximel fumarate for the treatment of adult patients with RRMS.

2.1.2. Epidemiology

Worldwide, the number of people with MS is estimated at 2.8 million. In 2020, the global incidence was estimated at 2.1 individuals per 100 000 and the global prevalence was estimated at 36 individuals per 100 000, with women being at a 2-times (in some countries at a 4-times) higher likelihood to develop MS than men[1]. Regionally, the median prevalence of MS in 2020 was greatest in Europe (143 per 100 000), followed by the Americas (117 per 100 000), and the Eastern Mediterranean (33 per 100 000). Prevalence of MS in Africa, South East Asia and Western Pacific was less than 10 per 100 000. Overall, the incidence of MS appears to increase over the years.

[1] Walton C, King R, et al. Rising prevalence of multiple sclerosis worldwide: Insights from the Atlas of MS, third edition. Multiple Sclerosis Journal. 2020;26(14):1816-1821.

2.1.3. Aetiology and pathogenesis

While the exact aetiology of MS remains unknown, it is generally assumed that MS is mediated by an immune-mediated inflammatory process that is triggered by environmental factors and superimposed on a genetic predisposition. The major contributors to this process are macrophages and microglia from the innate immune system, and T and B lymphocytes from the adaptive immune system. From the peripheral immune system, autoreactive T-helper cells are primed and stimulated to infiltrate the CNS where they target myelin antigens. Inflammation of the white and grey matter tissues in the CNS due to focal immune cell infiltration and release of cytokines are the incipient cause of tissue damage in MS not only to the myelin sheath but also to the underlying axons. This process happens over time and results in repeated attacks. Demyelination and axonal damage impair or interrupt nerve transmission, giving rise to clinical signs and symptoms. B and T cells, monocytes, natural killer cells, and dendritic cells are all involved in any stage of MS. Neuropathology studies have found that the patterns of inflammation are very similar between relapsing and progressive MS.

2.1.4. Clinical presentation and diagnosis

Symptoms of RRMS can include numbness and weakness in the legs leading to difficulty in walking, vision loss, incoordination, cognitive dysfunction, fatigue, and pain. These lesion-driven symptoms are also associated with considerable anxiety and distress for patients. Relapses may result in incomplete recovery of function and leave permanent disability and impairment that accumulates over time[2,3].

The diagnosis of RRMS can be based on clinical considerations alone, but magnetic resonance imaging (MRI), cerebrospinal fluid, and/or electrophysiological findings can support, supplement, or even replace some of the clinical diagnostic criteria for MS. Given the complexities of diagnosing MS, the McDonald diagnostic criteria have been developed and continue to be revised to facilitate earlier diagnosis and initiation of treatment. The McDonald diagnostic criteria comprise clinical observation, neurologic examination, brain and spinal cord MRI scans, visual/auditory evoked potentials, and cerebrospinal fluid examination[4]. These criteria have been used for nearly 2 decades and have recently been updated in 2017[4-7].

[2] Fred D. Lublin, Stephen C. Reingold, Chapter 2 Clinical Features and Subtypes of Multiple Sclerosis, Editor(s): W. Ian McDonald, John H. Noseworthy, Blue Books of Practical Neurology, Butterworth-Heinemann, Volume 27, 2003, Pages 13-20.
[3] Stoppe M, et al. Outcome of MS relapses in the era of disease-modifying therapy. BMC Neurol. 2017 Aug 7; 17(1):151.
[4] Thompson AJ, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018 Feb;17(2):162-173.
[5] McDonald WI, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. Ann Neurol. 2001 Jul;50(1):121-7.
[6] Polman CH, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". Ann Neurol. 2005 Dec;58(6):840-6.
[7] Polman CH, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol. 2011 Feb;69(2):292-302.

2.1.5. Management

In addition to medicines approved for the symptomatic treatment of MS (e.g., aminopyridine for improvement of walking ability) and for the treatment of relapses (such as corticosteroids), there are currently more than ten disease modifying treatments (DMTs) approved for use in patients with RRMS and/ or other forms of relapsing MS (RMS) in the EU. In a clinical setting, early treatment of RMS usually starts with a substance from the interferon-beta class (IFN-β), glatiramer acetate (GA), dimethyl fumarate [DMF], or teriflunomide. These medicines are characterised by moderate clinical efficacy (relative relapse reduction compared to placebo in the 30to 50% range) and are therefore typically used in patients without high disease activity.

A higher relative relapse reduction was found to be achieved by the S1P receptor modulator fingolimod, which is therefore approved for highly active RRMS only owing to its safety profile. Safety concerns with fingolimod include cardiac effects at treatment initiation, serious and opportunistic infections, progressive multifocal leukoencephalopathy (PML), cutaneous malignancies, lymphoma, macular oedema, posterior reversible encephalopathy, respiratory effects, increased liver enzymes, and the risk of rebound after stopping the treatment. Three drugs from the class of S1P receptor modulators have recently been approved, i.e., siponimod, ozanimod, and ponesimod. Siponimod is indicated for the treatment of adults with secondary progressive MS with active disease evidenced by relapses or imaging features of inflammatory activity. Ozanimod is indicated for the treatment of adult patients with RRMS with active disease as defined by clinical or imaging features. Ponesimod is indicated for the treatment of adult patients with RMS with active disease defined by clinical or imaging features.

The monoclonal DMTs anti CD-20, ocrelizumab and ofatumumab, are indicated for the treatment of adult patients with RMS with active disease defined by clinical or imaging features. Other DMTs including the monoclonal antibodies alemtuzumab and natalizumab, as well as cladribine, a nucleoside analogue of

deoxyadenosine, are restricted to patients with highly active disease due to less favourable safety profiles. Daclizumab was withdrawn from the market in 2018 due to serious safety concerns (cases of serious inflammatory brain disorders). The chemotherapeutic agent mitoxantrone is reserved for patients with high active MS without alternative treatment options.

2.2. About the product

Diroximel fumarate (DRF, also named Vumerity, BIIB098, ALKS 8700, and RDC-5108 in the dossier) is a fumarate ester that has been developed for the oral treatment of RRMS. DRF undergoes rapid pre-systemic esterase cleavage to produce the major active metabolite monomethyl fumarate (MMF). MMF is the active moiety of DMF (also termed BG00012) contained in the centrally authorised medicinal product Tecfidera (EMEA/H/C/2601). The applicant holds the Marketing Authorisation of Tecfidera, which is also indicated for the treatment of RRMS in adults.

In addition to MMF, the major inactive metabolite 2-hydroxyethyl succinimide (referred to as HES or RDC-6567) and the minor metabolite RDC-8439 (less than 1% of total DRF related systemic exposure in humans) are formed from DRF.

The mechanism by which DRF and DMF exert therapeutic effects in MS is not fully understood. Non-clinical studies indicate that DMF and DRF pharmacodynamic (PD) responses appear to be mediated, at least in part, through stimulation of nuclear factor (erythroid 2)-related factor 2 (Nrf2) transcriptional activity in the response to oxidative stress. DMF has been shown to up regulate Nrf2-dependent antioxidant genes in patients (e.g. NAD(P)H dehydrogenase, quinone 1; [NQO1]).

The claimed indication is *"treatment of adult patients with RRMS"*.

DRF has been formulated as hydroxypropyl methylcellulose (HPMC) hard capsules of a 231 mg strength. Accordingly, each minitablet contains 7 mg of DRF. Clinical therapy is proposed to be initiated with an oral dose of 231 mg twice a day (BID; *bis in die*) under supervision of a physician. After seven days, this dose should be increased to the oral maintenance treatment of 462 mg BID. An oral dose of 462 mg DRF and 240 mg DMF was found to produce bioequivalent exposure to MMF after administration in adults. Thus, it is expected that clinical efficacy and safety of both drug products are similar with equipotent dosing, i.e. 462 mg DRF twice daily equals 240 mg DMF twice daily.

2.3. Type of Application and aspects on development

DRF has been characterised in an extensive clinical pharmacology programme including ten Phase 1 studies in healthy subjects and special populations. Seven Phase 1 studies with DRF assessed the pharmacokinetics (PK), absorption, distribution, metabolism, and elimination (ADME), drug-drug interactions (DDIs), effects on cardiac repolarisation, and PK in participants with renal impairment. Three phase 1 studies aimed to establish relative bioavailability of MMF between DRF and DMF under fasted and fed conditions as well as with varying conditions of fat and caloric content.

The clinical development programme in MS patients consists of two Phase 3 studies, one of which being an active-controlled study and the other being open-label (OL).

One completed double-blind study aimed to evaluate the comparative gastrointestinal (GI) tolerability of DRF and DMF (Study A302 [EVOLVE-MS2]), and the ongoing OL safety study of DRF (Study A301 [EVOLVE-MS1]) examines longer treatment with DRF in rollovers from A302 and *de novo* patients.

Since no pivotal trial has been conducted with DRF, clinical efficacy and safety basically rely on four pivotal DMF studies already submitted and assessed in EMEA/H/C/002601 (i.e., Phase 2 Study C-1900,

Phase 3 Study 109MS301, Phase 3 Study 109MS302, efficacy and safety data of Phase 3 open label extension (OLE) Study 109MS303).

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as gastro-resistant hard capsules containing 231 mg of diroximel fumarate as active substance.

Other ingredients are:

Capsule contents: methacrylic acid-ethyl acrylate copolymer (1: 1) type A, crospovidone type A, microcrystalline cellulose, colloidal anhydrous silica, triethyl citrate, talc, and magnesium stearate.

Capsule shell: hypromellose, titanium dioxide (E171), potassium chloride, and carrageenan.

Capsule print: shellac, potassium hydroxide, and black iron oxide (E172).

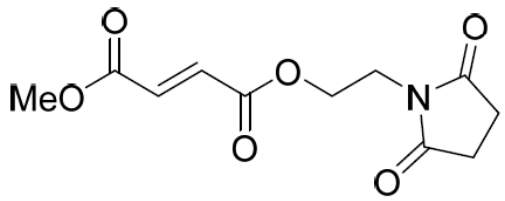
The product is packaged in HDPE bottle with a polypropylene child-resistant closure and a silica gel desiccant and available in packs of 120 (1 bottle) or 360 (3 bottles) capsules as described in Section 6.5 of the SmPC.

2.4.2. Active Substance

General information

The chemical name of the active substance is 4-*O*-[2-(2,5-dioxopyrrolidin-1-yl)ethyl] 1-*O*-methyl (*E*) but-2-enedioate corresponding to the molecular formula $C_{11}H_{13}NO_6$. It has a relative molecular mass of 255.22 g/mol and the following structure:

Figure 1: Active substance structure



The chemical structure of the active substance was elucidated by a combination of elemental analysis, infrared spectrometry (FTIR), NMR (^{1}H and ^{13}C), powder X-ray diffraction (PXRD), and mass spectrometry.

Diroximel fumarate is a white to off-white non-hygroscopic powder, the solubility in water is pH independent. It is slightly soluble across the pH range of 2 to 9 respectively at 20°C and at 37°C.

The active substance has a non-chiral molecular structure.

Diroximel fumarate exhibits polymorphism.

Manufacture, characterisation and process controls

Diroximel fumarate is produced by one manufacturer.

The manufacturing process of diroximel fumarate consists of three chemical transformation steps, recrystallisation steps and a milling step.

Possible organic impurities arising from the manufacturing process of the active substance have been adequately identified/characterised. The impurities were also evaluated for potential mutagenicity using both rule-based and statistical-based tools.

Concerning elemental impurities, analytical test results of six batches of diroximel fumarate by ICP-MS demonstrate absence (<LoQ) of elemental impurities in the active substance.

Information on the possible formation of organic impurities, including impurities originating from starting materials, has been provided.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

Solvent used for the manufacturing process and is controlled in accordance with criteria described in the ICH Q3C(R6) guideline.

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

Critical process parameters of the manufacturing process have been identified and adequate controls established. The specifications for the isolated intermediates implemented are adequate.

The development of the manufacturing process of diroximel fumarate has been adequately described. The development focused on optimising reagents, raw materials, processing conditions, and operational efficiency to accomplish the chemical transformations and purifications without making changes to the synthetic route. Proven acceptable ranges for the critical process parameters (e.g., hold temperature in step 1 and step 2) were established and have been justified. No design space is proposed. Changes introduced have been presented in sufficient detail and have been justified.

The active substance is stored in double food-grade, antistatic, low-density polyethylene sealed bags. The sealed bags are placed into high-density polyethylene (HDPE) drums with snap lids that are equipped with tamper evident seals. The packaging material is in compliance with EU Directives 2011/10/EC and amendments and Ph. Eur. 3.1.4.

Specification

The active substance specification includes tests for appearance (visual), identification (HPLC, FTIR), assay (HPLC), related impurities (HPLC), residue on ignition (sulfated ash, Ph. Eur.), residual solvents (HS-GS), and particle size (Laser diffraction).

Impurities are categorised as specified impurities with individual acceptance criteria and unspecified impurities.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis data of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 3 commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 36 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested: appearance, water content, assay, and related impurities. The analytical methods used were the same as for release and were stability indicating.

The results under both long-term and accelerated conditions showed little change and variability for all test parameters.

The stability results indicate that the active substance is sufficiently stable. The stability results justify the proposed retest period.

2.4.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product is presented as a white gastro-resistant hard capsule, size 0 (approximately 18 mm in length), printed with 'DRF 231 mg' in black ink. Each capsule enteric-coated minitablets designed to provide a delayed release (DR) profile.

The active substance is a white to off-white crystalline solid, slightly soluble in aqueous solutions across the pH range 2 to 9. Diroximel fumarate Form I is the only form observed during release and stability of representative active substance batches at all scales. The isolated active substance is milled to meet a particle size distribution range. The specification for particle size distribution is provided and justified.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The HMPC capsule shell, although not compendial, contains ingredients compliant with Ph. Eur standards. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

Excipient compatibility studies and physicochemical properties of the active substance were evaluated in order to prioritise the selection of excipients during formulation development. A number of excipients for each function in the formulation were assessed and the final excipients selected.

An assessment of compatibility of diroximel fumarate with each excipient in the finished product was performed. It was concluded that the excipients selected for use in the finished product formulation are compatible with diroximel fumarate.

Development of diroximel fumarate capsules progressed following the establishment of a quality target product profile (QTPP).

The composition was developed to meet quality attributes (QAs) established for each stage to ensure the product performed as intended. Quality attributes that impacted the quality, safety or efficacy of the finished product were deemed critical quality attributes (CQAs). There were 3 stages of formulation development:

Stage 1: development of the minitablet composition

Stage 2: development of the coating system

Stage 3: selection of the capsule shell.

Influence of the particle size distribution of the active substance on the quality of the finished product has been thoroughly investigated.

The objective for the manufacturing process development was to ensure that a robust, repeatable process was established to ensure the critical quality attributes (CQAs) of the finished product were consistently met.The primary packaging is a HDPE bottle with a polypropylene closure and a silica gel desiccant. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The finished product is manufactured in one manufacturing site

The manufacturing process consists of blending, tableting, coating and encapsulation steps. Validation of the finished product manufacturing process follows a 3-stage life cycle approach, which includes process design, process performance validation (which is otherwise known as process performance qualification (PPQ) and continued (ongoing) process verification. This ensures that product and process understanding, from development through the production of commercial batches, are incorporated as part of validation. The overall purpose of the validation programme is to provide a high degree of assurance that the product, when manufactured in accordance with pre-defined procedures will consistently comply with quality requirements.

All steps in the finished product manufacturing process were successfully validated for finished product batches. All process validation batches met the release specification. The process validation results demonstrate that each unit operation of the manufacturing process is in a state of control and demonstrates the manufacturing process consistently provides a finished product that meets its pre-defined acceptance criteria and product quality attributes

The in-process controls are adequate for this pharmaceutical form.

Product specification

The finished product release and shelf-life specifications includes appropriate tests for this kind of dosage form: description (visual), identification (HPLC-UV, Raman spectroscopy), assay (HPLC-UV), impurities (HPLC-UV), uniformity of dosage units (Ph. Eur.), dissolution (Ph. Eur.), water determination (Ph. Eur.), and residual solvent (HS-GC), and microbial limit tests (Ph. Eur.).

The finished product has been routinely monitored for impurities. Process impurities in the active substance are controlled by the active substance specifications. Potentially mutagenic impurities have been assessed and none have been identified.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on 7 batches using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data, it can be concluded that it is not necessary to include any elemental impurity control.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessaryThe analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the release specifications, through traditional final product release testing.

Stability of the product

Stability data from commercial scale batches of finished product stored for up to 24 months under long term conditions (25ºC / 60% RH) and for up to six months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, assay, impurities, water content, base phase dissolution and acid phase dissolution. The analytical procedures used are stability indicating.

There is no change in stability over time at long term storage for these quality attributes.

In accordance with the ICH Guideline Q1A (R2), stress studies were performed for the purpose of identifying the likely degradation products and demonstrating that the methods are stability indicating.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The results detailed showed that the DRF capsule finished product is not photo labile.

An in-use stability study was conducted in one batch.

Based on available stability data, the proposed shelf-life of two years and store below 25°C, store in the original bottle in order to protect from moisture, as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

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

During the assessment, information was requested as major objections. The applicant provided responses and all these issues were considered resolved.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.4.6. Recommendations for future quality development

Not applicable

2.5. Non-clinical aspects

2.5.1. Introduction

DRF is rapidly cleaved by esterases after oral ingestion thereby generating predominantly the metabolites MMF and HES, or to a minor extent, RDC 8439 and methanol. The major metabolite MMF is pharmacologically active and known to mediate the anti-inflammatory and immunomodulatory activity of DMF, a dimethyl ester of fumaric acid authorised for RRMS therapy since 2014 (EMEA/H/C/2601; "Tecfidera"). In contrast, HES was confirmed to be pharmacologically inactive, but its levels exceeded those of MMF after administration of the maximally recommended human DRF maintenance dose of 462 mg BID (maximum recommended human dose [MRHD]; ~6.2-fold higher maximum observed concentration [Cmax] and 21.3-fold higher Area under the plasma concentration-time curve from time zero to time of last measurable concentration [AUC_{last}] of HES than MMF). The pharmacological characteristics of the main metabolites MMF and HES were therefore non-clinically elucidated in relation to the parent compound DRF and also in comparison to DMF.

It has been earlier demonstrated during marketing authorisation application (MAA) of DMF in primary rat and human astrocytes, oligodendrocytes and hippocampal neurons as well as in experimental autoimmune encephalomyelitis (EAE) models in rats that MMF releases the ubiquitous transcription factor Nrf2 from constitutive repression by "*Kelch-like erythroid cell-derived protein with CNC homology-associated protein 1*" (Keap 1). As a consequence, Nrf2 translocates into the nucleus to induce the expression of anti-inflammatory, antioxidant and stress-related genes like NADPH dehydrogenase (NQO1), aldo-keto reductase family 1 member B8 (Akr1b8), haem oxygenase 1 (HO1) and oxidative stress induced growth inhibitor 1 (Osgin1). Accordingly, equimolar oral doses of 192.5 mg/kg DRF and 100 mg/kg DMF effectively induced the Nrf2-dependent expression of Akr1b8, HO1 and Osgin1 within two or six hours post administration in mice with quantitative differences in brain, spleen, jejunum and kidney, which correlated with MMF levels in these tissues.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

The primary PD *in vivo* activity of DRF was also investigated in comparison to MMF and DMF in the well-established EAE model of human MS in rats. The daily oral doses of 354 mg/kg DRF, 181 mg/kg MMF and 200 mg/kg DMF were administered from the day of EAE induction for 22 days and were selected to achieve comparable MMF exposure. Although the analysis of MMF plasma exposure in a subset of animals pointed towards approximately two-fold higher levels in the MMF group than in DRF- and DMF-treated animals, the development and severity of EAE disease symptoms (median day of EAE onset, mean maximum EAE score and mean EAE severity) were comparably delayed between DRF-, MMF- or DMF-treated animals.

2.5.2.2. Secondary pharmacodynamic studies

In secondary PD interaction studies, DRF and HES concentrations of 10 and 300 µM each did not unveil any relevant binding to a panel of 135 receptors, transporters and enzymes. A subsequent screen aimed to elucidate the effect of 450 µM MMF, HES and the MMF/HES combination on 148 biomarkers in 12 primary human cell cultures systems. MMF revealed the anticipated induction of inflammatory, immunomodulatory and tissue remodelling biomarkers and concomitantly inhibited the proliferation of B cells, coronary artery smooth muscle cells and fibroblasts. Moreover, MMF was cytotoxic to vascular endothelial cells and peripheral blood mononuclear cells. In contrast, HES was pharmacologically inactive in these cell cultures and did not alter the MMF activity as evident by the biomarker activation profile of the MMF/HES combination that was highly congruent with MMF incubation alone.

2.5.2.3. Safety pharmacology programme

The safety pharmacology of DRF was investigated in good laboratory practice (GLP) compliant core battery of studies in accordance with ICH S7A and S7B recommendations (CPMP/ICH/539/00 and CPMP/ICH/423/02). Cardiovascular endpoints were also evaluated in general repeat-dose toxicology studies in monkeys.

Up to 300 µM of either DRF or HES and even higher concentrations of up to 1500 µM MMF did not interfere with human ether-à-go-go related gene (hERG) currents *in vitro*. In conscious telemetered monkeys, oral 400 mg/kg DRF doses induced minor QTc prolongations (3 to 6 %), which did not correlate with the time of maximum concentration (t_{max}) of MMF or the minor metabolite RDC-8439 (~45 min each).

In rats, oral DRF doses up to 600 mg/kg did not impair respiratory function in a plethysmography study and did not affect CNS function in a fibreoptic bronchoscopy.

2.5.2.4. Pharmacodynamic drug interactions

No PD interaction studies have been performed with DRF, which is acceptable given the established primary and secondary pharmacodynamic as well as safety pharmacological effects of its active metabolite MMF and the available clinical experience with DMF in RRMS therapy, which was adequately considered for Section 4.5 of the SmPC.

2.5.3. Pharmacokinetics

The PK properties of DRF were determined in different cell types *in vitro* and after single and repeated once daily oral administration in rats and monkeys *in vivo* using validated liquid chromatography with tandem mass spectrometry. With regard to the previously licensed DMF ("Tecfidera"), DRF was similarly expected to be pre-systemically hydrolysed by esterases. The unspecific cleavage of the two ester bonds does not involve the main hepatic enzymes and is not subject to gender or species differences.

As in humans, the rapid metabolic conversion of DRF generally precluded its identification in animal plasma. Instead, drug exposure had to be monitored by means of the two major human metabolites MMF and HES that were also confirmed as main metabolites following repeated once daily oral administrations in rats and monkeys. In addition, the minor metabolite RDC-8439 (<1 % of drug related exposure in humans) was formed in minimal amounts in both species.

C_{max} of MMF and RDC-8439 were determined after 15 min in rats and after 45 minutes in monkeys, whereas the C_{max} of HES was evident between 45 min and 2 h. The exposure of MMF and HES increased dose-dependently in rats and even dose-proportionally in monkeys. Following five days of dosing, MMF and HES exposure had decreased in rats, but remained nearly constant in monkeys. As RDC-8439 concentrations were generally low in both species, the dose/exposure relationship is only implicated by its C_{max}, but could not be established for AUC.

Overall, none of the three metabolites accumulated in animals. The AUC-based exposure of HES in plasma exceeded that of MMF by 18.3- to 39.6-fold in rats and 7.2- to 16.9-fold in monkeys.

In accordance with data obtained during authorisation of DMF, MMF demonstrated low binding to plasma proteins in all species (≤27 %), which was even lower for HES and RDC-8439.

The tissue distribution was analysed after single oral administration of DRF by Quantitative Whole Body Autoradiography in pigmented rats using two radioactive variants that contained the ^{14}C-labels either inside the succinimide of the HES entity, or in the MMF moiety. Both substances were predominantly detected in the wall of urinary bladder and gastrointestinal tract as well as in kidney, aorta, liver and blood. However, more extensive distribution could be traced for the DRF substance with the radioactively labelled MMF moiety leading to substantial levels in brain, spinal cord, uveal tract, eye, lens, pigmented and non-pigmented skin, adrenal, pituitary and thyroid gland, fat, lymph node, spleen, thymus, heart, muscle, bone, Harderian, lachrymal and salivary glands. Except thymus and prostate, radioactivity within these tissues was detectable until study termination at 675 hours post dosing. In contrast, the DRF compound with the label inside the succinimide moiety subsided faster and was no longer measurable beyond the 168-hour time point. This finding corroborates that the HES metabolite does not accumulate.

DRF substance containing the radioactively labelled MMF moiety also distributed into pigmented ocular, cutaneous and adrenal tissues.

In the mass balance study in rats, MMF could only be determined at 0.5 hours after oral administration in plasma, but not later. Concomitantly, glucose was confirmed in plasma until 4 hours post dosing, while HES was quantifiable up to the 8-hour time point. Other metabolites including RDC 8439 were below detection limits. In concert with earlier findings of DMF, these results indicate the conversion of MMF into fumaric acid, which enters the highly conserved tricarboxylic acid (TCA) cycle resulting in the formation of glucose, water and carbon dioxide. Accordingly, a substantial amount of radioactively labelled DRF was eliminated by expired air (35.91 %). In addition, MMF and HES were found to be excreted via urine (75.75 %), while minimal amounts were cleared by faeces. Compared to MMF, HES represented the major urinary metabolite in rats (75.16 % vs. 12.33 %).

In PK drug interaction studies *in vitro*, DRF and its metabolites MMF, HES and RDC-8439 did not reveal clinically relevant interactions with the main Cytochrome P450 (CYP) enzymes and uptake or efflux transporters.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

Instead of single dose toxicity evaluations, dose escalations in monkeys and short-term dose-range findings in rats and monkeys to establish the MTD for subsequent toxicity studies were performed, which is endorsed given available data from the previously licensed DMF, the generally limited relevance of single dose toxicity investigations and prevailing European 3R principles (see EPAR of "Tecfidera" and EMA/CPMP/ICH/286/1995; EMA/CHMP/SWP/81714/2010; EMA/CHMP/CVMP/JEG-3Rs/450091/2012).

2.5.4.2. Repeat dose toxicity

The toxicity of DRF and its major metabolites MMF and HES was investigated after repeated oral administrations for up to 26 weeks in rats and 39 weeks in Cynomolgus monkeys, which were followed by recovery periods of 14 or 28 days to monitor the reversibility of effects. DRF was generally administered as oral gavage solution consisting of citrate buffered 0.5 % HPMC (Methocel E50 Premium LV™) and 0.2 % polysorbate 20, pH 4 ± 0.1, which differs from the clinical delayed-release gastro-resistant minitablet formulation in hard capsules that is intended for marketing.

Mortality or moribundity that could be attributed to DRF was limited to three male rats administered the 450 mg/kg/day high dose in the 91 days subchronic toxicity study with cardiac and adventitial inflammation as well as myocardial necrosis. All other fatalities in DRF-treated animals could be either ascribed to spontaneous tumours, inappropriate gavage administrations, or to erroneous blood sampling.

Across toxicity studies, the kidney was identified as toxicity target in rats and monkeys. The higher kidney weights correlated with proteinuria and corresponded histologically to adverse kidney tubular degeneration/necrosis, cortical tubular hypertrophy and/or regeneration upon chronic dosing of ≥50 mg/kg/day in monkeys and ≥100 mg/kg/day in rats. The impairments of renal tubular function were concomitantly indicated by increased urine volume, decreased urine specific gravity, dose-dependently elevated ratios of urinary biomarkers (albumin, KIM-1, NGAL, osteopontin, cystatin C) compared to creatinine and/or loss of urinary phosphorus, chloride and nitrogen. These renal tubular deficiencies only partially recovered within four weeks post dosing.

Moreover, DRF induced dose-dependent gastrointestinal disorders in rats and monkeys that resulted in reduced body weights of treated animals upon continuous DRF treatment. In rats, elevated stomach weights were determined at DRF doses ≥60 mg/kg/day, which were accompanied by hyperplasia of squamous mucosal epithelia in the non-glandular part of the stomach and duodenum at ≥150 mg/kg/day. At the highest DRF dose of 1000 mg/kg/day in a dose-range finding study in rats, severe stomach erosion/ulceration, inflammation, haemorrhage, moderate oedema, fibroplasia and/or luminal exudate were evident. The poor gastrointestinal tolerability of DRF in the toxicity investigations in monkeys was characterised by dose-dependent emesis/vomitus at ≥15 mg/kg/day, which was also observed in six out of eight control monkeys of the chronic toxicity study pointing towards a contributing role of the acidic vehicle formulation. Still, pathological changes were restricted to monkeys administered DRF and comprised stomach irritation, haemorrhage and inflammation as well as diarrhoea at ≥300 mg/kg/day. Similar to the non-glandular stomach counterpart in rats, minimal hyperplasia of

squamous epithelia were further eminent in oesophagus and/or tongue of monkeys at 400 mg/kg/day in the 14 days and ≥25 mg/kg/day in the 91 days toxicity studies.

Another common toxicity finding concerned the enlarged livers at DRF doses ≥100 mg/kg/day in toxicity studies in rats and at the 250 mg/kg/day high dose in the subchronic toxicity study in monkeys, which correlated with elevations of liver enzymes (alanine and aspartate aminotransferase and/or γ-glutamyltransferase) at higher dosages of ≥ 300 mg/kg/day in rats and the 1000 mg/kg/day top dose in monkeys. Triglyceride and cholesterol levels were additionally increased at lower doses of ≥ 50 mg/kg/day in rats and ≥250 mg/kg/day in monkeys. Liver effects generally emerged with dose- and time-dependent severity leading to incomplete reversibility after prolonged DRF administrations.

In the initial dose-finding study in rats, increased lymphocytes were determined at the 1000 mg/kg DRF maximum dose that could have represented an inflammatory response to the severe gastrointestinal effects at this level. In contrast, DRF reduced lymphoid counts in thymus and spleen of monkeys leading to decreased lymphocytes in circulation at 400 mg/kg/day. Lymphocyte reductions were also confirmed in thymus and spleen of dead or preterm sacrificed rats of the 91 days subchronic toxicity study. Partially reversible haemolysis (decreased red cell mass and myeloid/erythroid ratio, increased reticulocytes) was evident at ≥ 100 mg/kg/day in rats and monkeys and correlated with increased bilirubin at high dosages of 1000 mg/kg/day in rats and ≥300 mg/kg/day in monkeys.

Contrary to rats, five out of six monkeys administered the 250 mg/kg/day high dose in the 91 days subchronic toxicity study revealed mild physeal dysplasia due to chondrocyte hypertrophy and disorganisation in the proximal and distal femur as well as the proximal tibia. Physeal dysplasia did not reverse in one female in the recovery period and was therefore interpreted as adverse. No comparable findings were detected in rats or in monkeys during short-term administration of higher DRF dosages or following chronic treatment with lower doses.

2.5.4.3. Genotoxicity

The genotoxic potential of DRF was analysed in line with ICH S2(R1) requirements (EMA/CHMP/ICH/126642/2008), whereas MMF and HES were tested for mutagenicity and chromosomal aberrations *in vitro*. DRF, MMF and HES were not mutagenic in bacteria. In contrast to HES, DRF and MMF induced chromosomal aberrations *in vitro* at concentrations associated with >25% mitotic reduction. Nevertheless, DRF was negative in the bone marrow micronucleus assay *in vivo* and also did not provide relevant induction of DNA strand breaks in liver or duodenum cells in the Comet assay in rats.

2.5.4.4. Carcinogenicity

DRF was not tumorigenic in a 26 week study in transgenic Tg.rasH2 mice. In a two-year bioassay in rats, Leydig cell adenomas in male testis were significantly increased and considered DRF treatment related. Effects in seminiferous tubules are most likely a secondary effect of Leydig cell adenomas. The human relevance of Leydig cell adenomas in the testis of rats is likely limited but still unclear and the margin of exposure of MMF in rats compared to clinical exposure in humans is low at the no-observed-adverse-effect levels (NOAELs) for Leydig cell adenoma. In addition, kidney toxicities of dose-dependent severity were observed in mid and high dose males, which were interpreted as age-related chronic progressive nephropathy (CPN). Although CPN is common in aged rats, however, the effect was significantly increased in mid and high dose DRF groups and commonly noticed in other toxicity studies in rats and monkeys.

2.5.4.5. Reproductive and developmental toxicity

A complete set of reproduction and developmental toxicity studies has been performed with DRF under the current standards as per ICH S5 (R3) guideline (EMA/CHMP/ICH/544278/1998). These investigations included male and female fertility in rats, embryo-foetal development in rats and rabbits and pre-postnatal development in rats. In addition, the juvenile toxicity of DRF was studied for six weeks in rats.

DRF did not impair male and female fertility in rats at doses up to 400 mg/kg/day and 450 mg/kg/day, respectively, representing the NOAELs for male and female fertility. The AUC-based exposure margins of MMF and HES at these NOAELs compared to human levels at the MRHD were approximately 7× and 4× in male rats and approximately 9× and 4× in female rats, respectively. Slight increases in left epididymides weight and testes weight were each observed at doses ≥120 mg/kg and 400 mg/kg.

In the rat embryo-foetal developmental study, skeletal variations, including reduced ossification of the skull and vertebral arches, were seen in foetuses of dams treated with DRF at the highest dose of 400 mg/kg. At this dose level, maternal toxicity effects of decreased body weight due to lower food consumption and reduced foetal weight were noted. The NOAEL was 100 mg/kg, which corresponds to a minor two-fold AUC-based exposure margin of MMF and HES compared to human levels at the MRHD.

In the rabbit embryo-foetal developmental study, DRF-related maternal toxicity at the 350 mg/kg/day high dose comprised decreased defecation, body weight loss consequent to lower food consumption. In addition, abortion was noticed and three females had to be euthanised *in extremis*. Transient body weight loss and reduced food consumption were also seen in the 150 mg/kg/day mid dose group. Fetal examinations unveiled a higher incidence of post-implantation loss and subsequently lower mean litter proportion of viable fetuses in the 350 mg/kg dose group. Moreover, mean litter proportions of skeletal malformations were increased (vertebral centra anomaly, vertebral anomaly with associated rib anomaly and severely malaligned sternebra[e]) and skeletal variation (thirteenth full rib[s]). Skeletal malformations (vertebral centra anomaly and severely malaligned sternebra[e]) were also observed in three fetuses from a single litter of the mid dose group. At the NOAEL for maternal toxicity and embryo/fetal development of 50 mg/kg/day, the AUC-based exposure margins of MMF and HES were two-fold and 0.7-fold of human levels at the MRHD.

The placental transfer of MMF and HES following DRF administration has not been investigated in pregnant animals. Nonetheless, the passage of MMF across the placenta into foetal blood has been reported in female rats and rabbits, with a foetal to maternal plasma ratio of 0.48 to 0.64 and 0.1, respectively (see EPAR of "Tecfidera").

In the pre- and postnatal development study in rats, DRF-related decreases in pup birth weights and body weights/weight gains during the pre-weaning period were noted at the high dose of 400 mg/kg. Concomitantly, adverse treatment-related effects in F0 females included body weight loss and lower food consumption. No treatment-related adverse effects were observed on pre- and postnatal development (sexual maturation and neurobehaviour) and on reproduction of the F1 pups. Based on these findings, the NOAELs were 100 mg/kg/day for F0 females and 400 mg/kg/day for F1 pups. The AUC-based exposure margins of MMF and HES at the NOAELs compared to the human levels at the MRHD were three-fold and one-fold for F0 females and ten-fold and three-fold for F1 pups, respectively. Whereas DRF, MMF and RDC-8439 were not quantifiable in plasma of F1 pups, HES was determined on PND 4 and 10 with pup concentrations of approximately 2 – 6% and 0.2 – 3% of those in F0 females.

The excretion of DRF and its metabolites MMF, HES and HES into milk has not been investigated in animals. However, the above data suggest the transfer of HES to pups via breast milk in rats, whereas transfer of DRF, MMF and RDC-8439 via breast milk has not been demonstrated.

In the six-week repeated dose juvenile toxicity study in rats, DRF administration between PND 25 and 63, which corresponds to a human paediatric population of around 2-16 years old, did not affect development, behaviour or reproductive performance. With the exception of the effects on the bones (decreased femur size, mass, and density, changes in bone geometry), the target organ toxicities (renal tubule cell hypertrophy and hyperplasia of the non-glandular stomach) were comparable to those identified in DRF toxicity studies in adult rats. At the NOAEL in juvenile rats of 150 mg/kg/day, the AUC-based safety margin to human exposure at the MRHD for MMF and HES is 1.4-fold and 1.5-fold, respectively.

2.5.4.6. Toxicokinetic data

Toxicokinetic parameters were determined at the beginning and termination of the respective dosing phases of the subchronic and chronic toxicity studies in rats and monkeys. The DRF pro-drug was not quantifiable and the systemic exposure was primarily followed by means of MMF exposure. The inactive HES metabolite was only confirmed in chronic toxicity studies in rats and monkeys, because a validated analytical assay was not earlier established. Accordingly, the HES exposure had to be retrospectively estimated for shorter treatment durations by the help of bridging PK studies in both species that covered the respective toxicological dose ranges. Except fertility studies in male and female rats, toxicokinetic determinations generally revealed low safety margins of MMF and HES exposures at the NOAELs of standard toxicity, reproduction toxicity and carcinogenicity studies with regard to clinical levels of both major metabolites at the MRHD of DRF in humans.

2.5.4.7. Local tolerance

The local tolerance of an extended release minitablet formulation of DRF was investigated for 14 days in monkeys administered once daily oral doses of 125 or 375 mg as one capsule or 840 mg as two capsules, respectively. Apart from mild reversible signs of haemolysis at the mid and high dose level, no systemic toxicities were unveiled. This seems attributable to the fixed dose regimen, because the overall low number of monkeys with wide age and body weight range resulted in variations of body weight adjusted DRF doses and, hence, variable MMF exposures within study groups (e.g., the 840 mg/day high dose corresponded to approximately 100.5 to 218 mg/kg/day). In fact, a close inspection of the individual data in the corresponding study report revealed minimal but statistically significant higher weights of kidneys and liver in males of the mid and high dose groups, which had been similarly determined in repeated-dose toxicity studies of DRF and DMF in monkeys (see EPAR of "Tecfidera"). In addition, emesis/vomitus was seen in four out of six monkeys of the 840 mg/day extended release minitablet high dose group.

2.5.4.8. Other toxicity studies

Immunotoxicity

Lymphocyte declines were determined after oral DRF administration in subchronic toxicity studies in rats and monkeys and were similarly evident in clinical DRF studies, which has been adequately considered for risk minimisation measures (RMM) as previously approved for DMF.

Dependence

Secondary PD investigations did not indicate any interaction of DRF, MMF or HES with CNS targets associated with dependence. In addition, no CNS-related behavioural abnormalities or withdrawal symptoms were identified in the non-clinical programme of DRF.

Impurities

DRF substance containing the RDC-2239 impurity from an early manufacturing process was investigated at doses up to 600 mg/kg DRF and 9 mg/kg RDC-2239 in a 28-day repeat-dose toxicity study in rats in comparison to DRF material without this impurity. Systemic toxicities were highly coincident with previous observations at similar DRF dosages and treatment durations in other toxicity studies in this species, and therefore not related to the RDC-2239 impurity.

An unsaturated form of RDC-2239, named RDC-7935 was identified in the commercial DRF manufacturing process and did not reveal any specific findings when contained in the DRF test substance in the 14 days repeat-dose toxicity study in rats. Using allometric scaling and the NOAEL of 600 mg/kg/day of this toxicity study, the applicant aimed to derive an acceptable level of RDC-7935. Not all parameters of this calculation can be agreed, because a lower human body weight of just 50 kg seemed more appropriate. Nevertheless, appropriate RDC-7935 limit has been actually proposed for the drug substance specification of DRF and can therefore be accepted from a toxicological point of view.

Phototoxicity

DRF substance containing the radioactive label inside the MMF moiety distributed into pigmented ocular and cutaneous tissues, which suggests melanin-binding. Nonetheless, DRF and its metabolites MMF, HES and RDC-8439 do not pose any phototoxic potential.

2.5.5. Ecotoxicity/environmental risk assessment

As DRF is a prodrug that is rapidly converted to the active metabolite MMF, the provided environmental risk assessment has been conducted for MMF. Based on prevalence data in Phase I, the $PEC_{surface}$ water had been refined resulting in a value of 0.64 µg/l that exceeds the action limit of 0.01 µg/l. Therefore, a Phase II risk assessment was provided.

The results of the submitted studies demonstrate, that a bioaccumulation potential of MMF is not expected. MMF can be classified as readily biodegradable and thus, no further investigation of environmental fate properties is required. MMF is also not expected to enter surface water or accumulate in sediments and therefore, an environmental assessment of MMF in the sediment compartment in Tier B is not necessary. Furthermore, no risks for the aquatic environment and microorganisms had been identified for MMF.

Based on the provided studies/information it can be concluded that MMF is not expected to pose a risk to the environment.

Table 1: Summary of main results

Substance (INN/Invented Name): diroximel fumarate, prodrug of monomethyl fumarate					
CAS-number (if available): 2756-87-8					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	log Dow (pH 5) = -0.515 log Dow (pH 7) = -1.065 log Dow (pH 9) = -2.159			Potential PBT (N)
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, refined based on prevalence	0.64	µg/L			> 0.01 threshold (Y)
Other concerns (e.g. chemical class)	--	--			(N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	$K_{oc,\ sludge}$ = 26.0 & 59.6 L/kg			List all values
Ready Biodegradability Test	OECD 301	68 % (d 28), kSTP (1 h-1)			readily biodegradable
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *Raphidocelis subcapitata*	OECD 201	NOEC	3050	µg/L	species
Daphnia sp. Reproduction Test	OECD 211	NOEC	14000	µg/L	
Fish, Early Life Stage Toxicity Test/ *Pimephales promelas*	OECD 210	NOEC	≥8630	µg/L	species
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	1000000	µg/L	

2.5.6. Discussion on non-clinical aspects

Pharmacology

DRF is rapidly converted by ubiquitous esterases into the major metabolites MMF and HES. MMF was earlier established to mediate the immunomodulatory activity of DMF (EMEA/H/C/2601; "Tecfidera"). DRF, MMF and DMF comparably attenuated the development and severity of disabilities in the EAE model of human MS in rats. The MMF exposure of rats of the DRF group was approximately 11- to 13-fold and the HES exposure about 6.5- to 7-fold higher than the clinical C_{max} and AUC_{last} at the MRHD of 462 mg BID in RRMS patients.

Mechanistically, DMF was earlier shown to induce the expression of Nrf2-dependent target genes, which could be eliminated by either downregulation of Nrf2 transcripts with specific siRNA or in Nrf2 / knockout mice (see EPAR of "Tecfidera"). The induction of Nrf2 target genes by DMF in the EAE model in rats was associated with dose-dependent inhibition of demyelination, cellular degeneration and interference with the activation of astrocytes, macrophages and microglia. Meanwhile, the Nrf2 activation in human RRMS patients receiving DMF-therapy has been correlated with effective disease remission and the selective reduction of CD8+ T cells (Gopal S et al. 2017; Hammer A et al., 2018; Lückel C et al., 2019). The stimulation of Nrf2-dependent transcripts in concert with MMF levels by equimolar doses of DRF or dimethyl fumarate was confirmed in various tissues of mice, which indicates a comparable mechanistic basis of diroximel fumarate and dimethyl fumarate. The available knowledge on the mechanism of action of diroximel fumarate, MMF and dimethyl fumarate in animals and human patients is adequately reflected in Section 5.1 of the proposed SmPC.

DRF and HES concentrations of 10 and 300 µM each did not reveal any secondary PD interaction with 135 receptors, transporters and enzymes, which coincides with results obtained at up to 30 µM

concentrations of DMF and MMF after marketing authorisation of "Tecfidera" (EMEA/H/C/2601/II/61/G). A follow-up investigation analysing MMF, HES or the combination of both major metabolites in 12 primary human cell culture systems revealed the known pharmacological effects of MMF, whereas HES proved to be inactive and did not affect the activity of MMF. The maximum HES concentration of 450 µM tested in this screening study was approximately 5-fold above the clinical level of 92.2 µM at the C_{max} in RRMS patients receiving the MRHD (13.2 µg/ml). Thus, HES is considered pharmacologically inactive at the suggested clinical dosages.

In safety pharmacological investigations of cardiovascular function, DRF and HES did not inhibit hERG currents *in vitro*, whereas a single oral 400 mg/kg DRF dose mildly prolonged the QTc interval in telemetered monkeys (3 to 6 %). The MMF C_{max} and AUC_{0-24h} of the monkeys was > 30-fold and > 46-fold above clinical exposures of RRMS patients at the MRHD (MMF C_{max} of 2.11 µg/ml and AUC_{last} of 4.15 µg·h/ml, respectively). The HES exposure was not determined, but based on a bridging PK study, it can be assumed that the HES exposure was > 8-fold (C_{max}) and > 13-fold (AUC) above the levels in RRMS patients at the MRHD (C_{max} of 13.2 µg/ml and AUC_{last} of 88.6 µg·h/ml). In addition, the t_{max} of MMF or HES in monkeys renders any relationship unlikely. DRF is therefore considered to lack any clinically relevant arrhythmogenic potential, which coincides with existing non-clinical and clinical experience of DMF (see EPAR of Tecfidera). Nevertheless, all monkeys of the 400 mg/kg DRF high dose group vomited within 24 hours after administration, which matches the gastrointestinal intolerabilities at DMF doses ≥ 100 mg/kg in cardiovascular safety pharmacology studies in dogs known from the original MAA of Tecfidera or post-marketing (EPAR of "Tecfidera" and EMEA/H/C/2601/II/61/G).

Likewise, oral DRF doses up to 600 mg/kg did not affect respiratory or CNS function in rats. Due to the velocity of the pre-systemic esterase cleavage, the DRF plasma exposure could not be consistently determined. The MMF C_{max} and AUC_{0-24h} of the rats was > 20-fold above clinical levels of RRMS patients at the MRHD. Retrospective estimation of the HES exposure using pharmacokinetic determinations in rats suggests > 6-fold and > 13-fold higher C_{max} and AUC compared to levels in RRMS patients at the MRHD. The absence of any effect of DRF on respiratory or CNS function is consistent with earlier findings obtained with DMF or a mixture of DMF and various fumarate salts (Fumaderm, see EPAR of Tecfidera).

In view of these results from primary and secondary PD as well as safety pharmacology studies of DRF, MMF, and HES, further investigations including potential PD interactions are not deemed necessary, considering also the clinical experience from human RRMS therapy with DMF.

Pharmacokinetics

In accordance with previous knowledge from DMF (Tecfidera), DRF is rapidly and pre-systemically cleaved by non-specific esterases, which does not involve the main hepatic enzymes and is not subject to gender or species differences. It is therefore accepted that only male animals were evaluated in PK studies. The velocity of the ester bond cleavage of DRF interfered with the determination of its systemic exposure in animals.

As in humans, DRF was predominantly converted into the major metabolites MMF and HES in rats and monkeys. The AUC of HES was clearly higher than that of MMF in both species (18.3- to 39.6-fold in rats and 7.2- to 16.9-fold in monkeys), which covers the HES/MMF AUC ratio determined in plasma of RRMS patients after oral administration of the MRHD of 462 mg BID (21.3--fold. Both, MMF and HES extensively distributed throughout tissues of rats including pigmented ocular, cutaneous and adrenal structures that points towards melanin-binding (for evaluation of the phototoxic potential see below). The lack of information regarding the potential milk transfer of MMF or HES, which is also unknown from the earlier license of DMF (see SmPC of Tecfidera), was adequately considered for Section 4.6 of the proposed SmPC.

No accumulation of MMF or HES was found. In line with previous DMF results, MMF was further metabolised to fumaric acid that is subsequently transformed into glucose, water and carbon dioxide in the evolutionarily conserved TCA cycle across species. In the mass balance study in rats, significant amounts of the administered dose were consequently exhaled (35.91 %). HES was eliminated via urine to a considerably higher extent than MMF in rats (75.16 % vs. 12.33 %). The HES levels in human urine are similar (~58 to 63.4 %), while MMF is excreted in lower amounts (0.262 %). The principal clearance of DRF metabolites via the renal route compared to minimal amounts in faeces is consistent with DMF experience (see EPAR of "Tecfidera"; EMEA/H/C/2601).

In addition to the MMF and HES main metabolites, RDC-8439 was confirmed as minor metabolite in rats and monkeys. Thus, human metabolic profiles were adequately reflected in rats and monkeys to study the pharmacological and toxicological characteristics of DRF (see below).

Since DRF, MMF, HES and RDC 8439 did not show significant pharmacokinetic interactions with CYP enzymes, uptake or efflux transporters, the clinical risk for drug interactions after DRF dosing is regarded low, which is in line with current knowledge from therapeutic DMF administrations in RRMS and psoriasis patients (see EPAR and SmPC of Tecfidera, EMEA/H/C/2601, and Skilarence, EMEA/H/C/2157).

Toxicology

The toxicity of DRF, MMF and HES was studied in a stand-alone toxicology programme using rodent and non-rodent species that matched those previously tested for licensing of DMF (see EPAR of Tecfidera). The exposures of MMF and HES in animals were sufficient with respect to those in RRMS patients.

In the 91-day subchronic toxicity study in rats, 3 out of 15 males administered the 450 mg/kg/day DRF high dose died or had to be euthanised in extremis due to cardiac and adventitial inflammation with associated myocardial necrosis. These cardiac findings were similarly detected with minimal severity across all DRF dose groups in this subchronic toxicity study, the chronic toxicity as well as the carcinogenicity study of DRF in rats, but not in monkeys. In rats, these cardiac inflammations lack any obvious dose-response, could be also confirmed in vehicle-treated controls and were evident after either DRF, or DMF administration. An impact of HES on these cardiac toxicities is therefore unlikely. Instead, the cardiac changes appear to be attributable to common background lesions in rats that are exacerbated by the known renal toxicities of DRF and DMF, oxidative stress and prolonged study durations with concomitant aging of the animals (Chanut et al., 2013; Greaves, 2012). This assumption is supported by pertinent literature that even suggests a presumptive cardioprotective role of Nrf2 activation (Chen and Maltagliati, 2018). Further confidence is gained by the absence of a particular cardiac hazard in the clinical development of diroximel fumarate or since marketing authorisation of DMF (see EPAR and SmPC of "Tecfidera", EMEA/H/C/2601, and Skilarence, EMEA/H/C/2157).

As known from non-clinical and clinical experience with DMF (see EPAR and SmPC of Tecfidera and Skilarence), the kidney was the prominent toxicity target in rats and monkeys. The enlarged kidneys in both species were histologically associated with adverse kidney tubular degeneration/necrosis, cortical tubular hypertrophy and/or regeneration. The resulting impaired renal tubular function was evident by increased urine volume leading to increased excretion of urinary biomarkers and electrolytes and partially recovered upon cessation of dosing. The kidney toxicities developed at equivalent AUC-related MMF and HES exposure compared to human levels at the MRHD in both rats and monkeys. Still, there was no evidence for a contribution of long-term HES exposure to the kidney toxicities. Accordingly, the warnings and undesirable effects in Sections 4.4 and 4.8 of the proposed SmPC of DRF were aligned with those of Tecfidera.

Another characteristic toxicity target concerned the dose-dependent gastrointestinal disturbances in rats and monkeys, which had been comparably identified in animals and human patients receiving DMF (see

EPAR and SmPC of "Tecfidera" and "Skilarence"). The higher stomach weights of rats due to epithelial hyperplasia in the non-glandular part of the stomach/duodenum culminated in severe stomach erosion/ulceration, inflammation, haemorrhage, moderate oedema, fibroplasia and/or luminal exudate at the MTD of DRF. In safety pharmacological and toxicological investigations in monkeys, the gastrointestinal intolerabilities of DRF comprised dose-dependent emesis/vomitus at ≥15 mg/kg/day, which correlated with stomach irritation, haemorrhage and inflammation as well as diarrhoea at ≥300 mg/kg/day. Higher doses resulted in epithelial hyperplasia in oesophagus and tongue of monkeys, which corresponds to the aforementioned increased epithelial proliferation in the non-glandular stomach of rats and might be directly related to MMF-mediated stimulation of the transcriptional activity of Nrf2 (Motohashi et al., 2004). Of note, the change of the DRF oral gavage solution administered in toxicology studies to an extended-release DRF minitablet formulation still resulted in emesis/vomitus in 4 out of six monkeys administered the 840 mg/day high dose (approximately 100.5 to 218 mg/kg/day due to highly variable body weight) in a later 14 days multiple dose local tolerance study. In view of the gastrointestinal disturbances in rats and monkeys, no safety margin with regard to clinical exposure at the MRHD of DRF in RRMS patients could be established. Consequently, gastrointestinal disorders constitute common/very common adverse drug reactions (ADR) in humans (see clinical assessment and SmPC).

In accordance with earlier results obtained with DMF, dose-dependent liver hypertrophy was observed in association with elevated liver enzymes, triglycerides and cholesterol in rats and monkeys, which was incompletely reversible following prolonged DRF treatment. Compared to RRMS patients at the MRHD, the liver was affected at equivalent MMF and HES exposure in rats, whereas 4- to 15-fold safety margins might be deduced from the observations in monkeys. Nonetheless, a warning for drug-induced liver injury has been implemented into Section 4.4 of the proposed SmPC consistent with clinical experience of DMF, which is agreed (cf. SmPC of Tecfidera).

Furthermore, the haematological alterations noted after administration of DRF are comparably known from DMF treatments. Except lymphocyte increases at the MTD in rats that are attributable to severe gastrointestinal inflammations, DRF generally decreased lymphocytes in thymus, spleen and in circulation of rats and monkeys. Lymphopenia has been commonly observed during clinical RRMS therapy with DMF and involves reductions of CD4+ T helper cells and particularly CD8+ cytotoxic T cells, which possibly accounts for the higher susceptibility of these patients for opportunistic infections like herpes zoster or progressive multifocal leukoencephalopathy (EMEA/H/C/2601/II/63; Fleischer et al., 2018; Hammer et al., 2018; Lückel et al., 2019). As both DRF and DMF exert their anti-inflammatory activity via the identical major metabolite MMF, the applicant proposes the same risk minimisation measures for DRF as meanwhile implemented for DMF, which is supported in line with ICH S8 requirements (CHMP/167235/2004).

In addition, partially reversible haemolysis was determined in DRF-treated rats and monkeys, which corresponded to increased bilirubin at high dosages in these species. As these changes developed in the absence of relevant safety margins, regular monitoring of blood counts has already been considered for Section 4.4 of the SmPC in line with the established warning of Tecfidera, which is endorsed (cf. SmPC of Tecfidera).

At the 250 mg/kg DRF high dose in the 91 days subchronic toxicity study in monkeys, chondrocyte hypertrophy and disorganisation in femur and tibia led to mild physeal dysplasia that did not reverse in one female and was, hence, considered adverse. Physeal dysplasia was not identified in monkeys during short-term administration of higher dosages or upon long-term treatment with lower doses. It seems noteworthy that reduced femur length, bone mass and density were identified in juvenile rats administered the 600 mg/kg/day DRF high dose for six weeks, which mirrored the decreased bone mineralisation in juvenile rats following DMF doses of 140 mg/kg/day for nine weeks (see below). Although the impaired bone growth might be related to malnutrition and the elevated excretion of

electrolytes in the study animals due to the gastrointestinal and renal toxicity of DRF and DMF (see above), current scientific knowledge rather stressed the importance of balanced Nrf2 activation for normal bone homeostasis (Hyeon et al., 2013; Kim et al., 2014; Sun YX et al., 2015; Yamaguchi et al., 2018; Yin et al., 2020; Sánchez-de-Diego et al., 2021). Bone deficiencies are more likely to manifest at younger age, which could explain the occurrence in the tested pre-pubertal monkeys and possibly also juvenile rats of the DRF toxicology programme, but not in the more mature adult rats. Apparently, bone findings depend on the administered dose, the treatment duration and the age of the animals. As physeal dysplasia only developed with a 15-fold safety margin with regard to MMF exposure at the MRHD of DRF, no increased human risk is presently envisaged considering also the restriction of the proposed indication of DRF to adult RRMS patients. Moreover, physeal dysplasia determined in monkeys has been adequately delineated in Section 5.3 of the SmPC.

DRF, MMF and HES did not exhibit any mutagenic potential. Nonetheless, DRF and MMF, but not HES, induced chromosomal aberrations *in vitro* at concentrations associated with >25 % mitotic reduction. In the bone marrow and Comet assay *in vivo*, DRF did not induce micronuclei or strand breaks in liver and duodenum cells. Hence, DRF bares no clinically relevant genotoxic potential.

DRF was not tumorigenic in transgenic Tg.rasH2 mice, but significantly increased Leydig cell adenomas in the testes and possible secondary effects in seminiferous tubules in a two year bioassay in rats. The unknown human relevance of Leydig cell adenomas in the testis of rats and the low safety margin of MMF exposure in rats compared to levels at the MRHD in humans has been adequately reflected in Section 5.3 of the SmPC.

DRF did not impair male and female fertility in rats, but slight increases in the weight of left epididymides and testes were each observed at doses ≥120 mg/kg and 400 mg/kg. These changes were reported as unrelated to treatment, because they might have been secondary to DRF-related effects on body weight, did not occur in a dose-dependent manner, and/or mean absolute epididymis and testis weights at these dosage levels were similar to controls. Nevertheless, effects in the epididymides and/or testes (minimal germinal epithelial degeneration, increased incidence of giant spermatids, slight decrease in spermatids in the tubular epithelium, and reduced testes weight) were also observed in CByB6F1 mice (wild-type littermates of *ras*H2 transgenic mice) and the two year rat carcinogenicity study (increased incidence of testicular Leydig cell adenomas associated with increased incidence and severity of seminiferous tubule degeneration/atrophy in testes and oligospermia/germ cell debris in the epididymides) with DRF and have been also described for DMF (see EPAR of Tecfidera). Therefore, a relationship of the testes and epididymides effects in the male fertility study to DRF-treatment cannot be excluded. However, the effects were only slight, not considered adverse and did not impact on male fertility. Histopathology findings in reproductive organs other than those described in the testes have not been observed in repeat-dose toxicity or carcinogenicity studies.

The diminished ossification seen in the rat embryo-foetal developmental study might be attributable to the maternal toxicity, because delayed ossification as a result of maternal feeding restriction has been observed in rats (Nitzsche, 2017) and was similarly reported for DMF (see EPAR of Tecfidera).

A higher incidence of skeletal malformations and variation in rabbits treated with DRF in the embryo-foetal developmental study has been observed with little or no safety margin to human exposure at the NOAEL. At present, it cannot be excluded that the induction of skeletal malformations and variations in rabbits occurs via a direct effect of DRF and/or its metabolites. Since the incidence of skeletal malformations was low without evidence of a causative mechanism and since it occurred in rabbits only but not in rats, the human relevance of these findings is currently unknown, which has been appropriately considered for instructions in the SmPC and PL, respectively. Still, the potential human risk should be closely monitored in the pregnancy registry studies.

No DRF-related adverse effects (AEs) were observed on pre- and postnatal development in rats (sexual maturation and neurobehaviour) and on the reproduction of the F1 pups.

In juvenile rats, DRF administration between PND 25 and 63 also did not affect development, behaviour or reproductive performance and target organ toxicities matched those identified in adult rats (see above). Although some changes in the bones of juvenile rats may be associated with lower body weights, a direct effect of DRF on bone development cannot be excluded given the abnormal physeal dysplasia in Cynomolgus monkeys. These effects are of limited relevance for treatment of adult RRMS patients. The relevance for paediatric patients is currently unknown, which has been satisfactorily implemented into Section 5.3 of the SmPC.

DMF has been established to lack a clinically relevant dependence potential in self-administration and drug discrimination studies. As DRF and DMF solely act via the MMF metabolite, specific investigations of the dependence potential of DRF are therefore not required in accordance with the tiered approach of the pertinent European guideline (EMEA/CHMP/SWP/94227/2004).

In rats, DRF was found to distribute into melanin-containing pigmented ocular and cutaneous tissues. However, the applicant confirmed that DRF, MMF, HES and RDC-8439 do not absorb in the UV/visible light spectrum of 290 to 700 nm. For this reason, no further phototoxic testing in accordance with the tiered approach of the ICH S10 guideline is required (EMA/CHMP/ICH/752211/2012).

Considering the submitted data, DRF is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

The applicant had previously addressed all non-clinical concerns. Meanwhile, the SmPC and PL have been adequately revised in accordance with CHMP requests. For this reason, approval is recommended from a non-clinical perspective.

2.6. Clinical aspects

DRF has been developed for the treatment of RRMS.

The starting dose for diroximel fumarate is 231 mg twice a day orally. After seven days, the dose should be increased to the recommended maintenance dose of 462 mg DRF (administered as two 231 mg DRF capsules) twice a day orally. Temporary dose reductions to 231 mg DRF twice a day may be considered for individuals who do not tolerate the maintenance dose. Within one month, the recommended dose of 462 mg DRF twice a day should be resumed.

This MAA includes data for both DRF and DMF. The clinical efficacy and safety package relies primarily on DMF data already submitted and assessed by the EMA and ten completed Phase 1 studies and 1 completed and 1 ongoing Phase 3 studies with DRF.

2.6.1. Introduction

GCP aspects

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

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

- **Tabular overview of clinical studies**

Table 2: DRF summary of Phase 1 programme

Study Number	Study Description	Study Design	Participants	Endpoints
ALK8700-001	Evaluate the Safety and Tolerability of DRF After Oral administration in Healthy Adult Participants	Phase 1, double-blind, placebo-controlled; 3-part	Part 1: N = 56; Part 2: N = 16; Part 3: N = 32	Safety, tolerability, and PK
ALK8700-A102	Effect of Food on Single Dose; Safety, Tolerability and PK of Multiple Doses	Phase 1, double-blind, placebo-controlled; 2-part	Part A: N = 16; Part B: N = 60	AUC_{last}, C_{max}
ALK8700-A103	Bioavailability of MMF After a Single Dose of DRF or Tecfidera in Fasted Participants	Phase 1, double-blind crossover	N = 35	C_{max}, t_{max}, t_{lag}, $t_{½}$, AUC_{inf}, AUC_{last}, and safety assessments: AE reports, clinical laboratory results, vital signs, ECG results, and C-SSRS scores
ALK8700-A104	Bioavailability of MMF After a Single Dose of DRF or Tecfidera in Participants fed a HF Diet	Phase 1, double-blind, balanced crossover	N = 42	C_{max}, t_{max}, t_{lag}, $t_{½}$, AUC_{inf}, AUC_{last}
ALK8700-A105	Mass Balance Study of Single Doses of Unlabelled DRF With and Without Promoiety- labelled [^{14}C]-DRF in Healthy Males	Phase 1, open-label, fixed-sequence; 2-period	N = 10	Absorption, metabolism and excretion of unlabelled DRF, with and without promoiety labelled [^{14}C]-DRF Safety and tolerability of DRF
ALK8700-A106	Alcohol Dose-dumping Study to Determine the Influence of Coingestion of Alcohol on the PK of DRF in Healthy Participants	Phase 1, single-centre, open-label, randomised, 3-period, 6-sequence, crossover	N = 31	Concentrations of DRF and its relevant metabolites; AEs, vital signs, clinical laboratory parameters, ECG parameters and C-SSRS scores
ALK8700-A107	Digoxin DDI Study to Investigate the Effect of DRF on the PK of Digoxin	Phase 1, single-centre, open-label, sequential	N = 24	C_{max}, t_{max}, AUC_{inf}, AUC_{last}
ALK8700-A108	Renal Impairment study of the PK, Safety and Tolerability of DRF in Patients with Renal Impairment	Phase 1, open-label, multicentre	N = 32	Concentrations of DRF and its relevant metabolites, AEs, vital signs, clinical laboratory parameters, ECG parameters
ALK8700-A109	Evaluate the Comparative Bioavailability, Safety, and Tolerability of MMF After Administration of DRF and Tecfidera when Taken with Meals of Varying Fat and Caloric Content	Phase 1 bioavailability	N = 48	C_{max}, t_{max}, t_{lag}, AUC_{inf}, AUC_{last}
ALK8700-A110	Evaluate the Effect of Multiple Oral Doses of DRF on QTc Interval	Phase 1 tQT	N = 64	QTcF and heart rate, PR and QRS intervals, and T-wave morphology and U-wave presence

AE = adverse events; AUCinf = area under the concentration-time curve from time 0 to infinity; AUClast = area under the concentration-time curve from time 0 to time of the last measurable concentration; Cmax = maximum observed concentration; C-SSRS = Columbia Suicide Severity Rating Scale; DDI = drug-drug interaction; DMF = dimethyl fumarate; DRF = diroximel fumarate; ECG = electrocardiogram; HF = high-fat; MMF = monomethyl fumarate; PK = pharmacokinetic(s); tmax = time to reach maximum observed concentration; tlag = absorption lag time; t½ = elimination half-life; tQT = thorough QTc; PR = pulse rate; QTcF = QT interval corrected using Fridericia's formula; QTc = QT interval corrected

Table 3: DRF Phase 3 studies with clinical efficacy measures

Study Number (Study Status)	Study Population	Countries involved	Number of Participants	Study Phase and Study Design	Total Daily Dose	Efficacy Variables and Endpoints
A301 (Ongoing)	De novo: Male or female Age: 18 – 65 years RRMS: confirmed EDSS: 0.0 - 6.0 Neurologically stable No relapse for 30 days Rollover: Completed the full treatment period of Study A302	Belgium, Bulgaria, Canada, Germany, Poland, Russia, Serbia, Spain, Ukraine, United States	1057 (Enroled) 1057 (Safety) 1041 (FAS)	Phase 3 Multicentre, open-label. Evaluation of long-term safety and tolerability of DRF, administered up to 96 weeks	DRF, De novo: 462 mg (Week 1) 924 mg (Week 2+) DRF, Rollover: 924 mg (Week 1+)	MRI endpoints: GdE lesions, new or enlarging T2 hyperintense lesion count, total T2 hyperintense lesion volume and percent change, new unenhanced T1 hypointense lesions, and PBVC Clinical endpoints: EDSS score, participants with protocol-defined relapse, ARR, time to onset of 12-week confirmed disability progression, T25 FW score, and participants with NEDA-3 and NEDA-4 **REMARKS:** Study A301 is currently ongoing with an expected final CSR in Q2/2022. An interim CSR, including data through 07 February 2020, is included in the MAA A further interim CSR with data cut of 01 September 2020 was submitted during the MA review.
A302 Parts A and B (Completed)	Male or female Age: 18 – 65 years RRMS: confirmed EDSS: 0.0 - 6.0 Neurologically stable No relapse for 30 days	Germany, Poland, United States	506 (Enroled) 504 (Safety) 502 (FAS)	Phase 3 Multicentre, double-blind: DRF or DMF administered for 5 weeks Part A was exploratory. Part B was confirmatory.	DRF: 462 mg (Week 1) 924 mg (Week 2+) DMF: 240 mg (Week 1) 480 mg (Week 2+)	GI tolerability primary endpoint: - Number of days with any IGISIS individual symptom intensity score ≥ 2 relative to exposure days in Part A and Part B GI tolerability secondary endpoints: - Number of days with any IGISIS individual symptom intensity score: ≥ 2 relative to exposure days in Part B ≥ 1 and ≥ 3 relative to exposure days in Part A and Part B - Number of days with a GGISIS symptom intensity score ≥ 1, ≥ 2, ≥ 3 relative to exposure days in Part A and Part B - Worst IGISIS individual symptom intensity score by week during the exploratory GI tolerability endpoints: Number of days with any IGISIS individual symptom intensity score ≥ 1 and ≥ 3 relative to exposure days in Part B. Number of days with a GGISIS symptom intensity score ≥ 1, ≥ 2 and ≥ 3 relative to exposure days in Part B. Worst IGISIS individual symptom intensity score by week during the 5-week treatment period in Part B. Additional exploratory efficacy endpoints: EDSS score, participants with protocol-defined relapse, T25-FW score, SF-12 score, and EQ-5D-5L score

ARR = annualised relapse rate; DMF = dimethyl fumarate; DRF = diroximel fumarate; EDSS = Expanded Disability Status Scale; EQ-5D-5L = EuroQoL Group Health Outcome Measure 5-Level Version; FAS = full analysis set; GdE = gadolinium-enhancing; GGISIS = Global GI Symptom and Impact Scale; GI = gastrointestinal; IGISIS = Individual Gastrointestinal Symptom and Impact Scale; NEDA

= no evidence of disease activity; PBVC = percent brain volume change; RRMS = relapsing-remitting multiple sclerosis; SF-12 = 12-item Short-Form health survey; T25-FW = Timed 25-foot walk.

Table 4: DMF summary of clinical studies in support of the DRF application

Study Number	Study Description	Study Overview	Countries involved	Regulatory Status
C-1900	Double-Blind, Placebo-Controlled, Dose-Ranging Study to Determine the Efficacy and Safety of BG00012 in Participants with RRMS	In this dose-ranging study of 256 participants who received at least 1 dose of placebo or BG00012 120 mg QD, 120 mg TID, or 240 mg TID, BG00012 240 mg TID was determined to have a favourable benefit-risk profile and was selected for further clinical evaluation in the confirmatory, pivotal Phase 3 clinical studies.	United Kingdom, Germany, Netherlands, Czech Republic, Poland, Hungary, Switzerland, Turkey, Sweden, Russia	CSR submitted in Tecfidera MAA, approved 30 January 2014
109MS301 DEFINE	A Randomised, Multicentre, Double-Blind, Placebo-Controlled, Dose-Comparison Study to Determine the Efficacy and Safety of BG00012 in Participants With RRMS	In this study of 1237 randomised participants, treatment with BG00012 administered as 240 mg BID and TID over two years significantly reduced the occurrence of clinical exacerbations, reduced the risk of confirmed 12-week disability progression, and improved nearly all MRI measures of MS disease activity, compared with placebo.	Australia, Austria, Belgium, Bosnia and Herzegovina, Canada, Croatia, Czech Republic, France, Germany, Greece, Guatemala, India, Israel, Italy, Macedonia, Mexico, Moldova, Netherlands, New Zealand, Poland, Romania, Serbia, Slovakia, South Africa, Switzerland, Ukraine, United Kingdom, United States	CSR submitted in Tecfidera MAA, approved 30 January 2014
109MS302 CONFIRM	A Randomised, Multicentre, Placebo-Controlled and Active Reference (GA) Comparison Study to Evaluate the Efficacy and Safety of BG00012 in Participants With RRMS	In this study of 1430 randomised participants, treatment with BG00012, administered as 240 mg BID or TID significantly reduced clinical relapses over the two-year treatment period and improved nearly all MRI measures of disease activity, compared with placebo. A clinical meaningful reduction in disability progression was observed in both the BG00012 BID and TID groups, with reductions in the risk of confirmed disability progression.	Australia, Belarus, Belgium, Bosnia and Herzegovina, Bulgaria, Canada, Costa Rica, Croatia, Czech Republic, Estonia, France, Germany, Greece, India, Ireland, Israel, Latvia, Macedonia, Mexico, Moldova, New Zealand, Poland, Romania, Serbia, Slovakia, Spain, Ukraine, United States	CSR submitted in Tecfidera MAA, approved 30 January 2014
109MS202 FOCUS	Open-Label, Multicentre, Multiple-Dose Study of the Effect of BG00012 on MRI Lesions and PK in Paediatric Participants With RRMS Aged 10 to 17 Years	The PK, efficacy, and safety results in 22 paediatric participants in this study were consistent with the overall BG00012 dimethyl fumarate experience to date in adult healthy volunteers and adult participants with RRMS. In this study of 22 paediatric participants with RRMS, dimethyl fumarate administration during a 24-week Treatment Period was effective in reducing brain MRI lesions. PK parameters in paediatric and adult participants were comparable. The safety and tolerability profile of dimethyl fumarate was consistent with that observed in previously conducted studies in adult participants with RRMS. Resulted in an update to Sections 4.2, 4.8, 5.1, and 5.2 of the Tecfidera SmPC.		CSR submitted in II/0042, approved 09 November 2017
109MS303 ENDORSE	A Dose-Blind, Multicentre, Extension Study to Determine the Long-Term Safety and Efficacy of	In this long-term extension study (enrolling participants from MS301 and MS302) the majority of participants with an EDSS score ≤2 at baseline (n = 140) maintained walking abilities throughout 8	Australia, Austria, Belarus, Belgium, Bosnia and Herzegovina, Bulgaria, Canada, Croatia, Czech Republic, Estonia, France, Germany, Greece,	Final CSR dated 13 July 2020 included in Module 5.3.5.2.

Study Number	Study Description	Study Overview	Countries involved	Regulatory Status
	two Doses of BG00012 Monotherapy in Participants with RRMS	years, as indicated by EDSS score ≤3.5 (99%). In addition, approximately half of all participants were free from relapse and confirmed disability progression (continuous treatment with Tecfidera: 52.1% versus prior placebo treatment: 48.2%), demonstrating a sustained impact of Tecfidera on efficacy outcomes over a median of eight years.	Guatemala, India, Ireland, Israel, Italy, Latvia, Macedonia, Mexico, Moldova, Netherlands, New Zealand, Poland, Romania, Serbia, Slovakia, South Africa, Spain, Switzerland, Ukraine, United Kingdom, United States	
109MS311 CONNECTED	A Multicentre Extension Study to Determine the Long-Term Safety and Efficacy of BG00012 in Paediatric Participants With RRMS	This extension study (enrolling 20 participants from 109MS202) demonstrated Tecfidera's maintenance of effect in paediatric participants with RRMS over 96 weeks of treatment, adding to the findings seen in 109MS202, which demonstrated efficacy in reducing the incidence of new brain MRI lesions and relapses.	Belgium, Bulgaria, Czech Republic, Latvia, Turkey, United States, Poland, Lebanon, Kuwait, Germany	CSR submitted in P46/020 and II/0059, approved 25 July 2019

ALC = absolute lymphocyte count; ASA = acetylsalicylic acid; BID = twice daily; CD8+ = cluster of differentiation 8; CSR = clinical study report; DDI = drug-drug interaction; DMF = dimethyl fumarate; DNA = deoxyribonucleic acid; EDSS = Expanded Disability Status Scale; GA = glatiramer acetate; IFN = interferon; MAA = Marketing Authorisation Application; MMF = monomethyl fumarate; MRI = magnetic resonance imaging; MS = multiple sclerosis; PK = pharmacokinetic(s); QAM = once daily in the morning; QD = once daily; RNA = ribonucleic acid; RRMS = relapsing-remitting multiple sclerosis; SmPC = Summary of Product Characteristics; TCA = tricarboxylic acid; TID = three times daily.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

DRF (also referred to as ALKS 8700 and RDC-5108) is an orally administered fumarate ester that has been developed for the treatment RMS. DRF is a prodrug and its active moiety MMF is identical to that of the approved drug dimethyl fumarate (DRF; Tecfidera™).

The pharmacology of DRF and its metabolites was investigated in 13 clinical studies and two population PK (PopPK) analyses. The clinical studies include assessments of single- and multiple-dose PK, ADME, relative bioavailability, the effects of food, the impact of coingestion of alcohol, a thorough QT study, a renal impairment study, and a digoxin DDI study. In addition, four DMF clinical studies provided data that were relevant to the DRF clinical programme. These include an ADME study, 2 DDI studies, and a Phase 2 paediatric study.

The MAA for DRF relies on a PK bridging approach to Tecfidera (DMF). To make use of DMF efficacy, and to a lesser extent, safety data, bioequivalence had to be established. As both DRF and DMF undergo rapid presystemic hydrolysis to the active component MMF bioequivalence had to be established for the active moiety. MMF exposure (AUC and C_{max}) following administration of DRF 462 mg in the fasted state was shown to be bioequivalent to that following the administration of DMF 240 mg in the fasted state. There was also no clinically relevant impact on MMF AUC in the presence of a high-fat/high-calorie, medium-fat/medium-calorie, or low-fat/low-calorie meal. While there was a reduction in C_{max}, with the largest reduction observed with the high-fat/high-calorie meal, the C_{max} reduction observed with DRF was in line with the reduction observed with DMF 240 mg administered in the presence of high-fat/high-caloric meal. Therefore, DRF can be administered with or without food and in both cases shows equivalent exposure to DMF.

After oral administration DRF was almost completely absorbed. MMF concentration-time profiles displayed high inter- and intra-individual variability and irregular shape which may in part be due to

multiple absorption sites along the GI tract. PK parameter estimates are highly variable, with the exception of AUC. This indicates that, despite the high IIV and the irregular shapes of the concentration-time profiles, DRF administration yields stable and consistent MMF exposures.

DRF is immediately metabolised to the active moiety MMF and the primary, inactive metabolite HES and to a lesser extent another inactive metabolite, RDC-8439. Metabolism of MMF is well established and occurs via esterases followed by the TCA cycle, and the primary route of MMF elimination is exhalation of CO_2. MMF was eliminated rapidly from plasma with a mean half-life ($t_{½}$) of around 0.6 to 0.9 hours. HES is primarily excreted unchanged in urine and to a lesser extent further metabolised to two additional minor metabolites. HES was eliminated more slowly from plasma with a mean $t_{½}$ of around 8 to 22 hours.

MMF and HES exposures were dose-proportional after single and multiple doses. Minimal or no MMF accumulation (0.9- to 1.2-fold) was observed after BID dosing. HES exhibited a $t_{½}$ in plasma that was greater than the dosing interval, resulting in a 2.1- to 2.5-fold accumulation with BID administration of DRF. HES exposure was 10- to 13-fold greater than MMF exposure at steady state in healthy participants.

As expected, a renal impairment study found no influence of renal impairment on MMF exposure, the AUC of HES however increased with renal impairment severity. The popPK model predicts an about two-fold increase of steady state AUC, as the metabolite is however not active this is considered clinically not relevant.

A hepatic impairment study was not conducted, as the cytochrome system is not involved in DRF metabolism. The low DDI potential of DRF was confirmed in a series of *in vitro* inhibition and induction studies.

The popPK analyses revealed a correlation of clearance and volume of distribution with body weight. Thus, patients with lower body weight will show higher exposure at the same dose. This will be especially important in potential future dosing in paediatric patients.

In the thorough QT study, administration of multiple BID doses of DRF up to a supratherapeutic dose of 924 mg had no clinically significant effect on QTc interval.

2.6.2.2. Pharmacodynamics

The Application for DRF relies on a PK bridging approach to the authorised product Tecfidera®. Therefore, no new PD data were provided.

2.6.3. Discussion on clinical pharmacology

This MAA is based on a pharmacologic bridging approach to the authorised product DMF (Tecfidera®). Bioequivalence to DMF has been shown for the active moiety MMF. A similar food effect for both DRF and DMF could also be shown; therefore, DRF can be given with instructions for intake similar to Tecfidera®.

The inactive metabolite HES is only found when DRF is administered and not for DMF. In fact, due to its long $t_{½}$, it is the primary metabolite found in plasma at exposure 10- to 13-fold greater than MMF exposure at steady state. HES metabolism and excretion was therefore better characterised in a mass-balance study. It was found to be excreted primarily unchanged in urine and only undergoing minor additional metabolism.

MMF and HES pharmacology were further characterised in a renal impairment study. As expected, MMF PK was unchanged while a severity dependent increase in HES exposure was found. This is, however, considered not to be clinically relevant.

These key findings support that DRF can be given in bioequivalent doses, following the general recommendation for dosing and intake established for DMF (Tecfidera®).

2.6.4. Conclusions on clinical pharmacology

DRF pharmacology has been thoroughly investigated. The key findings support the authorisation in the same indication as DMF (Tecfidera).

2.6.5. Clinical efficacy

No formal efficacy studies using typical MS disease endpoints with DRF have been completed or are ongoing. Dedicated pivotal studies comparing head-to-head the efficacy of DRF and DMF in RRMS, using efficacy assessments relevant to MS primary endpoints have not been performed either. There are two Phase 3 studies (one completed) with DRF with exploratory efficacy clinical endpoints and MRI measurements. However, the total number of studies appears to be sufficient, taking into account that DRF is not a new active substance and the experience accumulated with DMF-MMF. DRF can be considered a prodrug leading to the main active moiety/metabolite, MMF, which has already been sufficiently investigated with DMF. In this AR, a presentation will follow with first the studies with DRF and then the main studies with DMF in a combined way and a joint presentation to the maximum possible extent.

2.6.5.1. Dose response studies

DRF Phase 1 clinical studies in healthy volunteers have shown that, at the investigative dose, DRF and DMF produce bioequivalent exposure to MMF, which are expected to result in similar efficacy and safety profiles.

Three Phase 1 bioavailability studies (ALK8700-A103, ALK8700-A104, and ALK8700-A109) provide sufficient data to establish comparability of the PK of MMF after oral administration of DRF and DMF under a number of dietary conditions. Exposure of MMF after a DRF dose of 462 mg was shown to be bioequivalent to MMF after the 240 mg dose of DMF under fasted conditions and after a high-fat meal. The C_{max} of MMF after a dose of DRF was highly variable, similar to that observed with DMF. Under all tested conditions, the C_{max} of MMF after a 462 mg dose of DRF was within the range of the C_{max} observed with 240 mg of DMF.

After a single oral dose of DRF, MMF showed a plasma exposure that was dose-proportional in the range of 49 to 980 mg. MMF exposure after multiple-dose administration of DRF also appeared to increase in a dose proportional manner across the dose range of 210, 420, and 630 mg.

Similarly, the dose proportionality analysis for HES in plasma after a single oral administration of DRF showed that plasma exposure was dose-proportional in the range of 49 to 980 mg. These results were also supported by multiple-dose results, which found that HES exposure appeared to increase in a dose proportional manner across the DRF dose range of 210, 420, and 630 mg.

Safety data from Phase 1 studies (Study ALK8700-001, ALK8700-A102, and ALK8700-A110) indicate that BID doses up to 924 mg were sufficiently well tolerated, with no relevant differences in safety or tolerability between single or repeated dosing at each level.

The selection of a 462 mg DRF maintenance dose was based on three comparative bioavailability studies (Studies ALK8700-A103, ALK87800-A104, and ALK8700-A109). DRF 462 mg and DMF at commercial doses (240mg) demonstrated bioequivalent exposure (AUC) of MMF across a variety of tested dietary

conditions. The effect of food on MMF PK after administration of DRF was very similar to the effect of food on DMF PK. MMF exposure after administration of DRF was consistent with exposure after DMF administration in the fasted condition.

2.6.5.2. Main studies

The Phase 3 clinical programme for DRF includes one completed Phase 3, double-blind study to evaluate the comparative GI tolerability of DRF and DMF (Study A302 [EVOLVE-MS2]) and one ongoing Phase 3, OL safety study of DRF (Study A301 [EVOLVE-MS1], ongoing).

Four DMF studies are particularly relevant in supporting the dosing, efficacy, and safety for DRF: a Phase 2 placebo-controlled dose-finding study for DMF (Study C-1900), a two-year, placebo-controlled Phase 3 study (Study 109MS301), a two-year, placebo-controlled Phase 3 study with an active comparator (Study 109MS302), and OLE study (Study109MS303). Study 109MS303 interim efficacy and safety data were submitted with the Tecfidera MAA and the final efficacy data are presented for the OLE of the study.

The primary evaluation of DRF efficacy is based on a PK bridging approach between DRF and DMF with respect to the active metabolite MMF, and no placebo-controlled clinical efficacy study with typical MS disease endpoints was conducted in the DRF clinical programme. Treatment effect over time is being assessed in the long term, OL Study A301 using exploratory efficacy, clinical, and MRI endpoints.

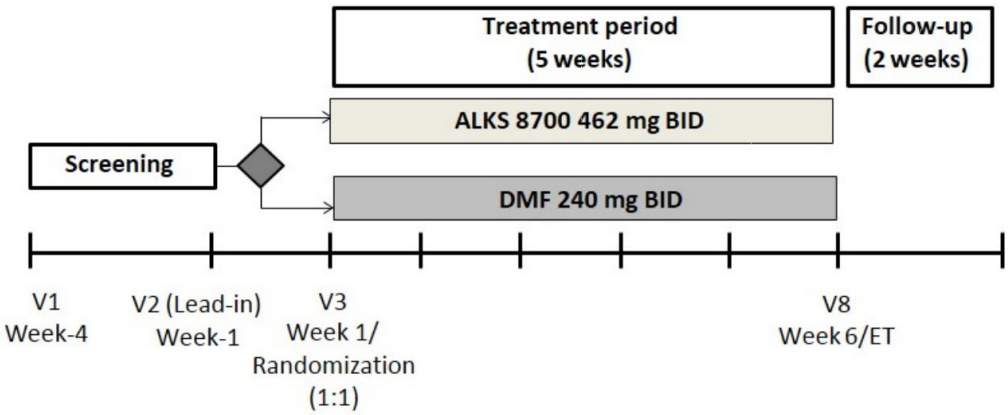
Study A302 (EVOLVE-MS-2)

This was a randomised, DB, Phase 3, multicentre study in adult participants with RRMS conducted in two parts for five weeks, designed to evaluate the GI tolerability of DRF compared to that of DMF using the Individual GI Symptom and Impact Scale (IGISIS) and the Global GI Symptom and Impact Scale (GGISIS) and to evaluate the safety and tolerability of DRF.

Methods (A302)

Parts A and B were identical in study design and included a five-week, DB treatment period with two blind treatment arms (DRF and DMF). The first 120 eligible participants were randomised to one of the two treatment groups in Part A (n = 60 per group).

Figure 2: Study A302 Design Schematic (Parts A and B)



BID=twice daily; DMF=dimethyl fumarate; ET=early termination; V=visit
Participants completing the 5-week treatment period either continued into the safety study A301 or entered the safety follow-up period and returned at Visit 9.

The study had an adaptive design such that data from Part A could be used to modify the GI tolerability endpoints and sample size in the study. Part A was exploratory. Following completion of Part A, the applicant conducted a planned, unblinded exploratory analysis of the Part A GI tolerability and safety data to inform the endpoint selection for the overall study. The statistical analysis plan (SAP) was updated following the review of Part A data. This adaptive approach was taken to better inform the sample size of Part B and the overall study analysis given that the endpoints were based on exploratory GI symptom scales that were being used for the first time

- **Study Participants (A302)**

The study included RRMS patients aged 18 to 65 years old with an EDSS between 0 and 6 at screening and at randomisation and neurologically stable with no evidence of relapse within 30 days prior to randomisation.

The first 120 eligible subjects were randomised to one of the two treatment groups in Part A (n=60 per group). Subjects who were randomised in Part A were not eligible to participate in Part B. Once randomisation for Part A was complete, the next 386 eligible subjects were randomised into one of the two treatment groups in Part B (194 subjects in the DRF group and 192 subjects in the DMF group). Subjects completing the entire five-week DB treatment in Parts A or B were eligible to roll over into the OL long-term safety Study A301. Subjects not rolling over to Study A301 completed a follow-up visit (Visit 9).

It is noted that due to the adaptive design, endpoints and sample size of Part B in Study A302 was finalised after the unblinded data from exploratory Part A had been examined. Upon identifying the primary endpoint, a sample size recalculation was conducted based on assumptions learned from Part A.

Due to the unblinded interim analysis after which the final version of the SAP was generated pooling of both parts cannot be accepted as a valid procedure. Only Part B data should be taken into account for the conclusions regarding the primary objective. The number of subjects in Part B, 386 in total (194 in the ALKS 8700 group and 192 in the DMF group) can be considered sufficient to allow for comparative results with DMF for short term GI tolerability.

- **Treatments (A302)**

Subjects meeting the eligibility criteria were randomised in a 1:1 ratio to 1 of 2 blind treatment groups, as follows:

- Group 1: DRF 462 mg BID, taken orally (with one-week titration)
- Group 2: DMF 240 mg BID, taken orally (with one-week titration)

In each part, both ALKS 8700 and DMF were administered orally BID as blinded study drug. Both ALKS 8700 462 mg BID and DMF 240 mg BID had an initial one-week dose titration period. Subjects were instructed to take study drug with or without food and to avoid taking study drug with a high-fat, high-calorie meal.

Table 5: Study drug dosing schedule (Parts A and B)

Blinded Treatment Group	**Week 1 (Days 1 to 7; 4 capsules per day)**	**Weeks 2 to 5 (Days 8 to 35; 4 capsules per day)**
ALKS 8700 462 mg BID (Total daily dose: 924 mg)	Morning: 1 capsule of 231 mg, 1 capsule of placebo Evening: 1 capsule of 231 mg, 1 capsule of placebo	Morning: 2 capsules of 231 mg Evening: 2 capsules of 231 mg
DMF 240 mg BID (Total daily dose: 480 mg)	Morning: 1 capsule of 120 mg, 1 capsule of placebo Evening: 1 capsule of 120 mg, 1 capsule of placebo	Morning: 1 capsule of 240 mg, 1 capsule of placebo Evening: 1 capsule of 240 mg, 1 capsule of placebo

BID=twice daily; DMF=dimethyl fumarate.

No dose reductions were permitted during the study. If a subject did not tolerate the study drug during the initial one-week dose titration period or after the dose titration period, the subject was discontinued from the study.

The study duration for both Parts A and B was in total approximately 11 weeks for all subjects in the US and approximately 11 weeks for male subjects and 13 weeks for female subjects in Poland and Germany. The study duration included up to four weeks for screening, including a one-week lead-in period (prior to randomisation), a five-week double-blind Treatment Period (including one-week titration), and up to two follow-up periods (a two-week follow-up [all subjects] and a four-week follow-up [female subjects in Poland and Germany only]) for subjects not continuing in the ALK8700-A301 long-term safety study.

Taking into consideration the available PK data, the outcome of the comparative bioavailability studies and the bioequivalence data with DMF, the doses and administration schemes are considered appropriate.

- **Objectives (A302)**

- To evaluate the utility of two GI symptom scales (IGISIS and GGISIS) and endpoints derived from the scales in assessing GI tolerability in adult subjects with RRMS after administration of ALKS 8700 or DMF in Part A
- To compare the GI tolerability of ALKS 8700 and DMF in adult subjects with RRMS using two GI symptom scales (IGISIS and GGISIS) with endpoints informed from Part A
- To evaluate the safety and tolerability of ALKS 8700 in adult subjects with RRMS in Parts A and B

The objectives of the study were not a direct comparison of DRF and DMF using relevant for MS efficacy endpoints. A different approach was followed by the applicant in an effort to show better GI tolerability

for DRF compared to DMF (see below). With respect to the scales used, please see comments in the Endpoints section.

- **Outcomes/endpoints (A302)**

Study A302 is primarily a safety study designed to evaluate the GI tolerability of DRF compared to that of DMF.

GI Tolerability endpoints

GI tolerability was determined using the IGISIS and GGISIS scales. According to the applicant, the IGISIS and GGISIS instruments were adapted from validated scales used to assess flushing in patients treated with niacin [Paolini 2008]. They were used in this study to assess GI tolerability in adult participants treated with DRF and DMF [Fox 2016].

The primary GI tolerability endpoint was the number of days with any IGISIS individual symptom intensity score ≥ 2 relative to exposure days in Part A and Part B.

The IGISIS is designed to assess the incidence, intensity, onset, duration, and functional impact of five individual GI symptoms: nausea, vomiting, upper abdominal pain, lower abdominal pain, and diarrhoea. Subjects rated the severity of each individual symptom via an 11-point numeric rating scale ranging from 0 (did not have) to 10 (extreme). Subjects rated how much each symptom interfered with their ability to accomplish their regular daily activities using a 5-point Likert scale ("Not at all" <"Slightly" < "Moderately" < "Quite a bit" < "Extremely"). An interference score is not reported for a symptom when the intensity score is 0 or if the symptom is still ongoing.

The GGISIS is a global scale to assess the overall intensity, bothersomeness, and functional impact of GI symptoms (nausea, vomiting, upper abdominal pain, lower abdominal pain, and diarrhoea) experienced during the previous 24 hours. Subjects rated the intensity and bothersomeness of GI symptoms via an 11-point numeric rating scale ranging from 0 (did not have) to 10 (extreme). Subjects rated how much each symptom interfered with their ability to accomplish their regular daily activities and, if employed, with their work productivity using 5 point Likert scales ("Not at all" <"Slightly" < "Moderately" < "Quite a bit" < "Extremely"). Subjects also indicated whether they were employed at the time of completing the GGISIS and, if employed, the hours of work missed due to GI symptoms during the past 24 hours.

The IGISIS and GGISIS were completed by subjects using e-diaries. Subjects completed both scales using e-diaries daily during a one-week lead-in period prior to randomisation (Visit 3) to facilitate familiarity with the scales as well as to evaluate for exclusionary GI symptomatology.

The GGISIS and IGISIS scales have been used similarly to the FSQ. During validation of the FSQ, the percentage of days with a score above a threshold of 1 and 4 were found to significantly discriminate among groups using FSQ. However, it is still unclear what difference between the assessed therapies constitutes a minimal significant clinical difference for IGISIS and GGISIS. The applicant has selected as endpoint the Number of Days with any IGISIS Symptom Intensity Score ≥ 2 relative to exposure days (which are approximately 35) and not ≥3, ≥ 4, ≥ 5 or ≥ 6. It should be noted that the Number of Days with any IGISIS Symptom Intensity Score ≥3 is below 1 for ALKS 8700 (DRF) (0.9) for Part A and B combined and Part B only (0.7). These numbers are very low to draw any clinically meaningful conclusions and are questioning the clinical usefulness of these scales.

Secondary GI tolerability endpoints included the following:

- Number of days with any IGISIS individual symptom intensity score ≥ 2 relative to exposure days in Part B

- Number of days with any IGISIS individual symptom intensity score ≥ 1 relative to exposure days in Part A and Part B
- Number of days with any IGISIS individual symptom intensity score ≥ 3 relative to exposure days in Part A and Part B
- Number of days with a GGISIS symptom intensity score ≥ 1 relative to exposure days in Part A and Part B
- Number of days with a GGISIS symptom intensity score ≥ 2 relative to exposure days in Part A and Part B
- Number of days with a GGISIS symptom intensity score ≥ 3 relative to exposure days in Part A and Part B
- Worst IGISIS individual symptom intensity score by week during the five-week treatment period in Part A and Part B

Exploratory Endpoints

- Number of days with any IGISIS individual symptom intensity score ≥1 relative to exposure days in Part B
- Number of days with any IGISIS individual symptom intensity score ≥3 relative to exposure days in Part B
- Number of days with a GGISIS symptom intensity score ≥1 relative to exposure days in Part B
- Number of days with a GGISIS symptom intensity score ≥2 relative to exposure days in Part B
- Number of days with a GGISIS symptom intensity score ≥3 relative to exposure days in Part B
- Worst IGISIS individual symptom intensity score by week during the 5-week Treatment Period in Part B

Other Assessments

Treatment effect over time was also assessed in an exploratory manner using the following (details of these structured interviews and questionnaires are provided in the protocol):

- Kurtzke Expanded Disability Status Scale (EDSS): This scale is used to measure and evaluate the level of functioning of patients with MS. Categories include ambulatory ability and Functional System scores: pyramidal (motor function); cerebellar; brainstem; sensory; bowel and bladder; visual; cerebral or mental; and other. The EDSS provides a total score on a scale that ranges from 0 to 10. The first levels 1.0 to 4.5 refer to people with a high degree of ambulatory ability and the subsequent levels 5.0 to 9.5 refer to the loss of ambulatory ability. The Functional Systems are scored on a scale of 0 (low level of problems) to 5 (high level of problems) to best reflect the level of disability observed clinically.
- MS Relapse: Protocol-defined relapse is described in the protocol.
- Timed 25-foot walk (T25-FW): The T25-FW (Kaufman et al, 2000) is a reliable quantitative mobility and leg function performance test based on a timed 25-foot walk.
- 12-item Short-Form health survey (SF-12): Quality of life was assessed using the SF-12 Version 2.
- EuroQoL Group Health Outcome Measure 5-Level Version (EQ-5D-5L): This measure is designed to assess decrements in health, based on a descriptive system that defines health in terms of five dimensions: Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression.

Given the short duration of this study, the primary reason for including the EDSS, T25-FW, SF-12, and EQ-5D-5L assessments was to obtain pre-treatment baseline values for participants who rolled over from this study into the A301 study. Changes from baseline for EDSS, T25-FW, SF-12, and EQ-5D-5L scores over a 5-week treatment period were not expected to be clinically meaningful.

It should be noted that with respect to the other endpoints, MS relevant assessments using EDSS, T25-FW, SF-12, and EQ-5D-5L were not expected to be clinically meaningful given the short duration of the study, as admitted by the applicant. However, some indications on the efficacy of DRF in MS could be obtained. These assessments could be considered supportive, complement the bioequivalence studies and provide further support for the approval of DRF based on DMF efficacy data.

Analysis of MRI Endpoints

Baseline MRI parameters (number of gadolinium-enhancing (GdE) lesions, GdE lesion number category [0, 1 through 4, 5 through 8, and ≥ 9], T2 lesion volume, and normalised brain volume) were summarised by treatment group and overall.

Safety throughout the study was assessed using the following: AEs, Vital signs (oral temperature, respiratory rate, heart rate, and blood pressure), clinical laboratory parameters (blood biochemistry, haematology, and urinalysis [including urine albumin, urine beta-2-microglobulin, and urine creatinine]), Electrocardiogram (ECG) parameters (uncorrected QT, QT interval corrected using Fridericia's formula, QT interval corrected using Bazett's formula, PR, RR, and QRS intervals), Columbia-Suicide Severity Rating Scale (C-SSRS).

- **Randomisation and Blinding (masking) (A302)**

This was a randomised DB study.

- **Statistical methods (A302)**

The study had an adaptive design such that data from Part A could be used to modify the GI tolerability endpoints and sample size in the study. Following completion of Part A, the applicant conducted a planned, unblinded exploratory analysis of the Part A GI tolerability and safety data to inform the endpoint selection for the overall study. The SAP was updated following the review of Part A data. This adaptive approach was taken to better inform the sample size of Part B and the overall study analysis given that the endpoints were based on exploratory GI symptom scales that were being used for the first time. This clinical study report presents the combined final results of Parts A and B.

In general, summary statistics (n, mean, standard deviation [SD], median, minimum, and maximum values for continuous variables, and number and percentage of subjects in each category for categorical variables) are provided by treatment group for evaluated variables. All summary tables were based on observed data, and missing values were not imputed unless otherwise indicated.

Measurements collected from unscheduled visits or repeated assessments were not included in the by-visit summary tables or figures but were included in the analyses for the potentially clinically significant (PCS) postbaseline values and subject listings. Source data for summary tables and statistical analyses are presented as by-subject data listings.

Baseline value was defined as the last non-missing assessment prior to the first dose of study drug. All statistical tests and confidence intervals (CIs), unless stated otherwise, are two-sided and set at 0.05 level of significance.

All of the efficacy analyses were summarised by the planned treatment assignment, and all of the safety analyses were summarised by the actual treatment.

The data were summarised for the following two study periods as appropriate:

- Treatment Period, which was defined as the period between the first dose date after randomisation and the last dose date plus 1 day, inclusive.
- Follow-up period, which was defined as the period between the last dose date plus 2 days and the last study date.

The number of days with any IGISIS individual symptom intensity score ≥ 2 (event days) is counted among observed diaries. Exposure days are the number of days between a subject's first dose date and last dose date during treatment period, inclusive. Let θ (1) and θ (2) denote the mean number of days with any IGISIS individual symptom intensity scores ≥ 2, for ALKS 8700 and DMF, respectively. Comparison of GI tolerability will be tested at 5% level of significance in a two-sided test, through the following hypothesis of no treatment effect:

H_0: θ (1) = θ (2) vs. H_a: θ (1) $\neq \theta$ (2)

ALKS 8700 will be claimed superior to DMF if the estimated θ (1) is less than the estimated θ (2) and p-value is less than 0.05 (in a 2-sided test). DMF will be claimed superior to ALKS-8700 if the estimated θ (2) is less than the estimated θ (1) and p-value is less than 0.05 (in a 2-sided test).

Event days will be analysed by the negative binomial regression model, including treatment as factor and adjusting for study parts (not included in part B only analyses), region (US and non-US), age and Body Mass Index (BMI). Additional covariates may also be included in the model. The logarithmic transformation of exposure days will be included in the model as the "offset" parameter. If the data are underdispersed, or if the negative binomial regression model does not converge, a Poisson regression model with the same covariates will be used instead of the negative binomial regression model. Dispersion will be evaluated from the Pearson Chi-square statistic. If the ratio of the Pearson Chi-square statistic to the degrees of freedom is ≤ 1 which indicates no overdispersion, then a Poisson regression model with adjustment for underdispersion will be used. Count distributions in which the number of intervals with zero events is higher than predicted by a Negative binomial or Poisson model may be modelled using a Zero-inflated model.

This method will also be used for the secondary endpoints by setting the GI symptom intensity score cut off as one and three. Empirical cumulative distribution function plot of number of event days by treatment groups will be presented.

Worst IGISIS symptom intensity score by week during the five-week treatment period:

Worst individual IGISIS symptom intensity score is defined as a subject's worst (i.e., highest) symptom intensity score for any symptom out of all completed IGISIS diaries during a given period. Worst IGISIS symptom intensity scores by week during the five-week treatment period for each subject will be summarised by treatment groups and will be analysed using an Analysis of covariance (ANCOVA) model. The model will include treatment as factors, and adjusting for study parts, region (US and non-US), age and BMI. Additional covariates may also be included.

Worst IGISIS individual symptom interference level:

Worst IGISIS individual symptom interference level is defined as a subject's worst symptom interference level (No symptom < Not at all < Slightly < Moderately < Quite a bit < Extremely) for a particular symptom out of all completed IGISIS diaries during the treatment period. All five GI symptoms (nausea, vomiting, upper abdominal pain, lower abdominal pain and diarrhoea) will be reported separately and summarised by treatment groups.

Sensitivity Analysis of IGISIS Endpoints:

An evaluable diary is defined as an instance when a subject took study drug prior to completing the diary and completed the diary within the recommended reporting window (two to nine hours post dose).

Summary statistics were presented for IGISIS primary and secondary endpoint by evaluable and non-evaluable dairies. Event days will be analysed controlling for evaluable and non-evaluable dairies.

The primary analysis based on Part A and Part B data is not acceptable due to the unblinded interim analysis with a potential type-1 error inflation and the finalisation of the SAP after the interim analysis. The analysis of the pooled data could therefore be biased. Instead, Part B should be considered only.

The main analysis (if based on Part B data), i.e., the use of a negative binomial model for the number of days with any symptom intensity score ≥ 2 using the log number of exposure days as an offset parameter is acceptable in general. However, the analysis was not clearly specified with respect to potential additional covariates. In addition, it is not clear whether the envisaged conditional procedure where the use of the model depends on the outcome still maintains the type-1 error, although inflation may not be considerable. This may, however, not be considered as a relevant issue since the negative binomial model was finally used with the initially planned covariates.

The applicant provided sensitivity analyses based on the proposed Poisson model with adjustment for overdispersion and the zero-inflated negative binomial model and these analyses showed comparable results with the primary analysis.

Furthermore, as the covariates were not properly pre-specified in the SAP (and age was added as an additional covariate), the analysis cannot be considered as fully pre-specified. The applicant provided an analysis without the factor age as a covariate as well as additional sensitivity analyses with added relevant baseline covariates. Despite that the analyses were not properly pre-specified the results from the provided additional sensitivity analyses were in line with the primary analysis.

In the IGISIS scale, if a symptom was assessed as ongoing, it was only recorded in the initial intensity score. Therefore, the applicant was asked to comment on which of the analysed parameters of the IGISIS scale allowed for the assessment of the severity of the side effects, which increased in intensity over time (A302). It was clarified that if an IGISIS symptom was recorded as ongoing, the intensity for an ongoing symptom was assumed to be unchanged and the initial intensity score collected at the symptom start time/date was carried over until the symptom ended or symptom severity changed. An example was given by the applicant whereby a participant records an ongoing symptom of nausea in the morning diary with an intensity score of 3 and over the course of the day this nausea is worsened, then the participant is asked to end the previous nausea symptom and enter a new nausea symptom with a newly categorised intensity score (for example, 6). This procedure may not be a true reflection of the clinical condition of the patient. It does not truly represent the worsening or the deterioration of the symptom and may provide a false picture of the symptom, introducing a bias. The same applies to recording a lower intensity score for a symptom that improves.

The applicant clarified how many event days were counted when a patient recorded more than 1 symptoms in a day with a symptom score ≥ 2 and how many event days were counted in case a symptom ended in the afternoon and another symptom started. This case is counted as 1 event day, the same as in the case of one symptom having a score ≥ 2 in a day (**Table 6**).

Table 6: Scenarios showing how event days were counted if a symptom ended in the afternoon and another symptom started later that day

Scenario[a]	**Symptom Score for Event Ending in the Afternoon**	**Symptom Score for New Symptom Later That Day**	**Number of Event Days**
Both symptoms have a score < 2	1	1	0
One symptom has a score < 2 and the other symptom has a score ≥ 2	1	4[b]	1
Both symptoms have a score ≥ 2	2[b]	6[b]	1
One symptom has a score ≥ 2	3[b]	1	1

[a] To simplify these scenarios, other symptoms collected on the Individual Gastrointestinal Symptom Impact Scale (IGISIS) questionnaire had a score of 0 and are not included in the table.
[b] Symptom score ≥ 2 therefore counted as an 'event day'.

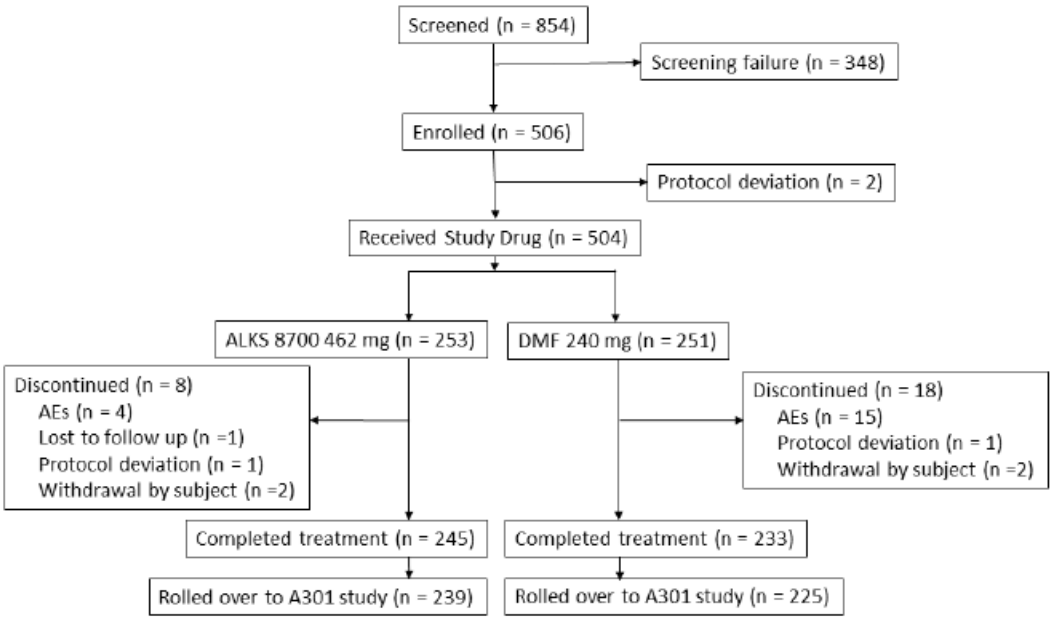
The main issue in the analysis, however, is based on the improper handling of missing evaluable diaries. For a considerable number of days the diaries were not evaluable or valid, which may also include completely missing diaries. No missing data imputation was neither planned nor performed for these days. Basically, the analysis was based on the assumption that the absence of a valid diary (or evaluability of a diary) was completely at random and the actual endpoint refers to a mixture of the presence of relevant symptoms (≥ 2) and the evaluability of the diary.

Hence, the applicant was requested to justify the validity and robustness of the conclusions with respect to the large number of non-evaluable diaries and whether the actual analysis yields an unbiased estimation for the relative reduction in days with any symptom intensity score ≥ 2, if all diaries were evaluable. According to the applicant, the percentage of non-evaluable diaries was balanced between the two treatment groups (31% for DRF, 27% for DMF) and the outcome from the two sensitivity analyses to assess the impact of the non-evaluable diaries did not appear to yield a biased estimation, which could have impacted the conclusions. However, the robustness of the analysis regarding the large amount of non-evaluable diaries still remains unclear since it still remains unclear whether reference-based multiple imputation was performed appropriately. The applicant wrote that "five repetitions were obtained for analyses *to show robustness* of the missing imputation of the difference of treatment effect on the number of days with IGISIS symptom intensity score ≥ 2". However, multiple imputation would require the combination of multiply imputed datasets applying Rubin's rule. Hence, the results given by the applicant cannot be assessed properly.

Results

- **Participant flow**

Figure 3: Subject Disposition (Parts A and B)



Abbreviations: AE=adverse event; DMF=dimethyl fumarate; n=number of subjects.

- **Recruitment**

The study was conducted at 70 sites (59 sites in the United States [US], 5 sites in Germany, and 6 sites in Poland), 59 of which enrolled subjects for Part A (53 sites in the US, 0 sites in Germany, and 6 sites in Poland).

First subject first visit: 15 March 2017 and last subject last visit: 27 June 2019

- **Conduct of the study**

Protocol amendments

The original protocol was finalised on 08 February 2016. There was one amendment that introduced no major changes. There were no changes in planned analyses from the protocol.

Protocol deviations

In total, there were 58 major protocol deviations (**Table 7**). According to the applicant, the protocol deviations were not considered to have a significant impact on the study results or the overall analysis of the data

Table 7: Reasons of protocol deviations

Reasons of protocol deviations	**Part A**	**Part B**
Did not Meet the Inclusion / Exclusion Criteria	4	3
Received Prohibited Medications	1	
Lack of Adherence with Study Medication	3	4
Randomisation or Dosing Error	10	13
Other Major Protocol Deviations	11	9
Total	29	29

- **Baseline data (A302)**

The mean age of subjects was 43.7 years, with most subjects (64.7%) being ≥ 40 years of age. The majority of subjects were female (72.8%), White (91.1%), and not Hispanic or Latino (97.0%). Approximately half of the subjects participating in this study were enrolled from the US (55.2% [278/504] of subjects). Mean (SD) BMI was 27.4 (6.0) kg/m2 (range: 17.1 to 54.3 kg/m2). The demographics and baseline characteristics were balanced between the two treatment groups.

Table 8 summarises baseline disease characteristics of the subjects in the Safety population. The mean values for disease characteristics were similar between the two treatment groups at baseline.

Table 8: Summary of baseline disease characteristics (Safety Population, Parts A and B)

Category	**Treatment Groups**		**All Subjects (N=504)**
	ALKS-8700 8700 (N=253)	**DMF (N=251)**	
Time Since MS Diagnosis (years)			
N	253	251	504
Mean (SD)	7.4 (7.80)	7.9 (7.37)	7.7 (7.58)
Time Since MS Onset (years)			
n	253	251	504
Mean (SD)	9.6 (8.96)	10.1 (8.55)	9.8 (8.76)
Number of Prior DMT(s)[a]			
n	253	251	504
Mean (SD)	1.3 (1.22)	1.3 (1.24)	1.3 (1.23)
Number of Prior DMT(s), n (%)			
0	84 (33.2)	85 (33.9)	169 (33.5)
1	73 (28.9)	72 (28.7)	145 (28.8)
2	60 (23.7)	43 (17.1)	103 (20.4)
≥3	36 (14.2)	51 (20.3)	87 (17.3)
Relapses in Previous 12 Months			
n	253	251	504
Mean (SD)	0.6 (0.72)	0.6 (0.72)	0.6 (0.72)
EDSS Score			
n	253	251	504
Mean (SD)	2.70 (1.407)	2.72 (1.380)	2.71 (1.392)
EDSS Score, n (%)			
0	7 (2.8)	8 (3.2)	15 (3.0)
1.0 or 1.5	56 (22.1)	51 (20.3)	107 (21.2)
2.0 or 2.5	79 (31.2)	80 (31.9)	159 (31.5)
3.0 or 3.5	60 (23.7)	63 (25.1)	123 (24.4)
4.0 or 4.5	26 (10.3)	24 (9.6)	50 (9.9)

Category	Treatment Groups		All Subjects (N=504)
	ALKS-8700 8700 (N=253)	DMF (N=251)	
≥5.0	25 (9.9)	25 (10.0)	50 (9.9)
Number of GdE Lesions			
n	251	251	502
Mean (SD)	0.9 (2.22)	1.1 (2.76)	1.0 (2.50)
Number of GdE Lesions, n (%)			
0 lesions	180 (71.1)	175 (69.7)	355 (70.4)
1-4 lesions	52 (20.6)	55 (21.9)	107 (21.2)
5-8 lesions	13 (5.1)	11 (4.4)	24 (4.8)
≥9 lesions	6 (2.4)	10 (4.0)	16 (3.2)
Unknown	2 (0.8)	0	2 (0.4)
T2 Lesion Volume (cc)			
n	252	251	503
Mean (SD)	13.168 (13.847)	12.132 (13.410)	12.651 (13.627)
Normalised Brain Volume (L)			
n	252	251	503
Mean (SD)	1.437 (0.084)	1.438 (0.077)	1.438 (0.080)

DMF=dimethyl fumarate; DMT=disease-modifying treatment; eCRF=electronic case report form; EDSS=Expanded Disability Status Scale; GdE=gadolinium-enhancing; Max=maximum; Min=minimum; MRI=magnetic resonance imaging; MS=multiple sclerosis; N=total number of subjects; n=number of subjects; SD=standard deviation.
a If multiple DMTs were reported with different verbatim drug names on the eCRFs for a given subject, they were counted as different individual DMTs.
Note: A non-DMT of "Medrol" was mistakenly reported for one subject enrolled in the ALKS 8700 group during Part A.
Note: One subject in the ALKS-8700 group did not have a baseline MRI due to an error at the MRI facility, and another subject in the ALKS-8700 group did not have baseline GdE lesion information due to unanalysable results.

There are no noticeable differences in baseline disease characteristics between the DRF and DMF treatment groups. There was a small imbalance in the GdE 5-8 and ≥9 lesions between DFR and DMF, if these groups were considered separately. However, if the 5-8 and ≥9 lesions were considered as one group then ≥5 lesions were 19 for ALKS 8700 (DRF) and 21 for DMF.

- **Numbers analysed (A302)**

Table 9: Summary of data sets analysed (Parts A and B)

Category	Treatment Group		All Subjects
	ALKS-8700	DMF	
Subjects Enrolled/Randomised, n	254	252	506
Subjects in the Safety Population, n	253 (99.6)	251 (99.6)	504 (99.6)
Subjects in the FAS Population, n (%)	253 (99.6)	249 (99.2)	502 (99.2)
Subjects in the PK Population, n (%)	4 (1.6)	0	4 (0.8)

DMF=dimethyl fumarate; ALKS-8700=diroximel fumarate; FAS=Full Analysis Set; n=number of subjects; PK=pharmacokinetic.

The safety population includes all enrolled subjects who received at least one dose of study drug during the DB Treatment Period. Only two subjects were not included in the Safety population analysis (due to protocol deviations that did not allow them to be allocated to a treatment group). A very small number of subjects (n=2) in the safety population who did not have at least one postbaseline GI tolerability assessment (GGISIS or IGISIS) on or before last dose date were not included in the full analysis set (FAS).

There were four major protocol deviations for Part A and 3 for Part B who did not meet the exclusion/inclusion criteria. The applicant confirmed that the two subjects, who were not included in the Safety population, could not be allocated to a treatment group.

- **Outcomes and estimation**

Of the 506 randomised subjects, 504 received at least one dose of study treatment, 502 subjects were included in the FAS population (253 subjects in the DRF group and 249 subjects in the DMF group).

Primary Endpoint

The mean (SD) values of event days for observed diaries (i.e., all diaries collected, without imputation of any values) were 1.5 (2.85) days and 2.5 (4.68) days for the DRF and DMF groups, respectively. The rate obtained from the negative binomial regression model is an adjustment to the mean number of event days after considering the subject's exposure days and adjusting for study parts, region (US and non-US), age, and BMI. The rate (0.041) for the DRF group was lower than the rate (0.076) for the DMF group. The rate ratio was 0.542 (95% CI [0.390, 0.754]) with a corresponding p=0.0003, representing a relative reduction of 45.8% in the DRF group compared with the DMF group.

Table 10: Summary of number of days with any IGISIS symptoms intensity score ≥ 2 (FAS population, pooled parts A and B)

Category	**Treatment Groups**	
	ALKS-8700 (DRF) (N = 253)	**DMF (N = 249)**
Number of Days with Any IGISIS Symptom Intensity Score ≥ 2, Observed Diaries		
N	253	249
Mean (SD)	1.5 (2.85)	2.5 (4.68)
Median	0.0	1.0
Min, Max	0, 19	0, 34
Number of Days of Exposure, Treatment Duration[a]		
N	253	249
Mean (SD)	35.2 (4.16)	34.2 (5.93)
Median	36.0	35.0
Min, Max	3, 45	1, 42
Analysis Results		
Rate (95% CI)	0.041 (0.032, 0.053)	0.076 (0.059, 0.097)
Rate ratio (95% CI)	**0.542** (0.390, 0.754)	
p-value	0.0003	

a Treatment duration = last dose date – first dose date + 1.
Note: Number of event days was analysed by a negative binomial regression model, with the logarithmic transformation of the number of exposure days as the 'offset' parameter and treatment group as a factor and adjusting for study part, region (US and non-US), age, and BMI. DMF was used as a reference group.

In addition, according to the applicant, Part B results were consistent with the pooled results and were similarly significant, including for the primary endpoint and for the originally proposed primary endpoint assessed in Part A (any IGISIS individual symptom intensity score ≥ 3; p =0.012) before the unblinded interim analysis and subsequent revisions to the study endpoints. Although not all secondary endpoints for the study were statistically significant (e.g., the number of days with a GGISIS symptom intensity score ≥ 2 or ≥ 3), they were all directionally concordant with the overall findings in favour of DRF.

Table 11: Summary of number of days with any IGISIS symptom intensity score ≥2 (FAS population, part B)

Category	Treatment Groups	
	ALKS-8700 (DRF) (N=253)	**DMF (N=249)**
Number of Days with Any IGISIS Symptom Intensity Score ≥ 2, Observed Diaries		
n	194	191
Mean (SD)	1.3 (2.70)	2.2 (4.22)
Median	0.0	0.0
Min, Max	0, 19	0, 34
Number of Days of Exposure, Treatment Duration[a]		
n	194	191
Mean (SD)	35.2 (3.80)	33.7 (6.31)
Median	36.0	35.0
Min, Max	3, 43	1, 42
Analysis Results[b]		
Rate (95% CI)	0.033 (0.025, 0.043)	0.063 (0.049, 0.082)
Rate ratio (95% CI)	**0.520** (0.356, 0.760)	
P-value	0.0007	

ALK-8700 = diroximel fumarate BMI = body mass index; C I= confidence interval; DMF=dimethyl fumarate; FAS = Full Analysis Set; IGISIS = Individual Gastrointestinal Symptom and Impact Scale; Max = maximum; Min = minimum; N = total number of subjects; n = number of subjects; SD = standard deviation; US = United States.
a Treatment Duration = last dose date – first dose date +1.
b Number of event days is analysed by a negative binomial regression model, with the logarithmic transformation of the number of exposure days as the "offset" parameter and treatment group as a factor and adjusting for study part, region (US and non-US), age, and BMI. DMF is used as a reference group.

The ratio results have been adjusted to participant's exposure days, study parts, region, age and BMI, but this adjustment has not been unambiguously pre-specified in the SAP stating that "additional covariates may also be included" (actually, age was included as a covariate), see also the corresponding comment in the assessment of the statistical methods.

Statistically significant differences have been demonstrated for the primary endpoint, Number of Days With Any IGISIS Symptoms Intensity Score ≥ 2, in the FAS populations for the pooled Part A and B (0.542, p = 0.0003) and for part B only (0.520, p = 0.0007). It is noted that Part B results (key secondary endpoint) were significant and consistent with the pooled results.

With respect to the GI tolerability AEs, in study A302 Part A and B, overall GI adverse reactions were observed in 34.8% of DRF-treated patients and in 49.0% of DMF-treated patients. Slightly more subjects on DMF discontinued due to TEAEs as compared with subjects on DRF (6% vs. 1.6%). However, and in order to put the percentages in a numerical perspective, four subjects on ALKS-8700 (DRF) discontinued the study due to adverse events and 15 subjects in the DMF group. From these discontinuations, 0.8% in ALKS-8700 (DRF) were due to GI disorders, whilst in the case of DMF group these were 4.8%. Out of these, one subject on ALKS-8700 (DRF) discontinued due to diarrhoea and one due to vomiting. In the case of DMF five subjects discontinued due to upper abdominal pain, three due to diarrhoea, three due to abdominal pain, two due to vomiting, one due to abdominal distention, one due to gastrointestinal pain and one due to nausea. An analysis for the discontinuations in Part B alone could have provided additional information, but the numbers are very low to allow any meaningful conclusions.

The specificity was moderate (59%). Furthermore, when the number of days with any IGISIS score ≥ 4, ≥ 5, ≥ 6 were evaluated the numbers were below unit 1 in both groups ALKS-8700 (DRF) and DMF showing that the numbers are very low to draw any clinically meaningful conclusions and questioning the clinical usefulness of these scales.

Finally, the mechanism for better DRF GI tolerance is unclear. Both DMF and DRF undergo pre-systemic hydrolysis with an identical active metabolite (MMF). According to the applicant's declarations, the primary metabolite of DRF, HES is inactive. Therefore, the applicant was requested to justify what mechanism lies behind the better tolerance of DRF.

The applicant presented a discussion of the probable basis for the better tolerability of DRF relative to DMF. Among the likely reasons for better gastrointestinal-related tolerance were the lower concentration of methanol formed, the larger particle size of DRF limiting binding to receptors within the gastrointestinal tract, and the lower electrophilicity of DRF. Nevertheless, all of the reasons raised by the applicant are considered speculative. There is no evidence to support that any of the presented mechanisms are important in the hypothesised better tolerance of DRF.

Secondary Endpoints

The assessment of the secondary endpoints provided either statistically significant results (differences of the worst overall intensity scores during the five-week treatment period in Parts A and B for the individual symptoms of nausea, vomiting and upper abdominal pain, IGISIS Intensity Score ≥ 1 in the Overall Population, IGISIS Intensity Score ≥ 3 in the Overall Population and Number of Days With a GGISIS Symptom Intensity Score ≥ 1) or a trend in favour of DRF (number of days with a GGISIS Symptom Intensity Score of ≥ 2 and number of days with a GGISIS Symptom Intensity Score of ≥ 3).

It is noted that the rate of discontinuations in the DMF group was consistent with what has been previously reported for DMF i.e. the most commonly reported adverse reactions leading to discontinuation (incidence >1%) in subjects treated with Tecfidera were flushing (3%) and gastrointestinal events (4%) [Tecfidera SmPC 2020]. This is indicative of the consistency of the results obtained up to now.

A useful secondary endpoint was the Worst IGISIS Individual Symptom Intensity Score during the five-Week Treatment Period. From the individual efficacy response data listing it appears that only a limited number of participants reported intensity scores of 7 (n=7), 8 (n=9), 9 (n=4) and 10 (n=12). The worst score 10 in most of the cases was used for diarrhoea followed by abdominal pain. This is also confirmed by the applicant’s analysis in which the symptom with the mean highest intensity score was diarrhoea (1.1 for DRF and 1.3 for DMF).

The limited number of patients reporting intensity scores ≥ 7 could be reassuring that subjects were not suffering to the degree that they could not report their symptoms and scores in their e-Diaries. From this it can be assumed that any missing values were unlikely to be due to a symptom and its respective high intensity e.g., diarrhoea 10.

Exploratory and other endpoints

In the case of the exploratory and other endpoints, which were typical MS relevant endpoints, it was anticipated that no meaningful differences could be observed between the two treatments, DMF and DRF, due to the short duration of the study. However, it is noted that the two treatments (despite the short duration of 12 weeks) behaved similarly i.e. EDSS (mean and median), T25-FW, SF-12, EQ-5D-5L scores at baseline and their change from baseline were similar between ALKS 8700 (DRF) and DMF.

- **Ancillary analyses (A302)**

The sensitivity analyses of the primary endpoint [number of evaluable days with any IGISIS symptom intensity score ≥ 2 (FAS Population, Parts A and B)] corroborated the primary analysis of the primary endpoint and showed statistically significant differentiation between treatment groups. Statistical significance was greater using evaluable days ($p < 0.0001$ and rate ratio 0.486) compared to the non-evaluable days analysis, which also demonstrated statistical significance, $p = 0.0479$ (rate ratio 0.640). Both analyses showed statistically significant differentiation.

The sensitivity analysis performed for the secondary endpoint [number of evaluable days with any IGISIS symptom intensity score ≥ 2 (FAS Population, Part B)] corroborated the primary analysis of this secondary endpoint. The rate ratio for the number of evaluable days (0.462) was statistically significant (p = 0.0005), but the rate ratio (0.630) for the number of non-evaluable days was not (p = 0.0963).

Study A301 (EVOLVE-MS-1)

A Phase 3 multicentre open label study to evaluate the long-term safety and tolerability of ALKS-8700 in adults with RRMS.

Methods (A301)

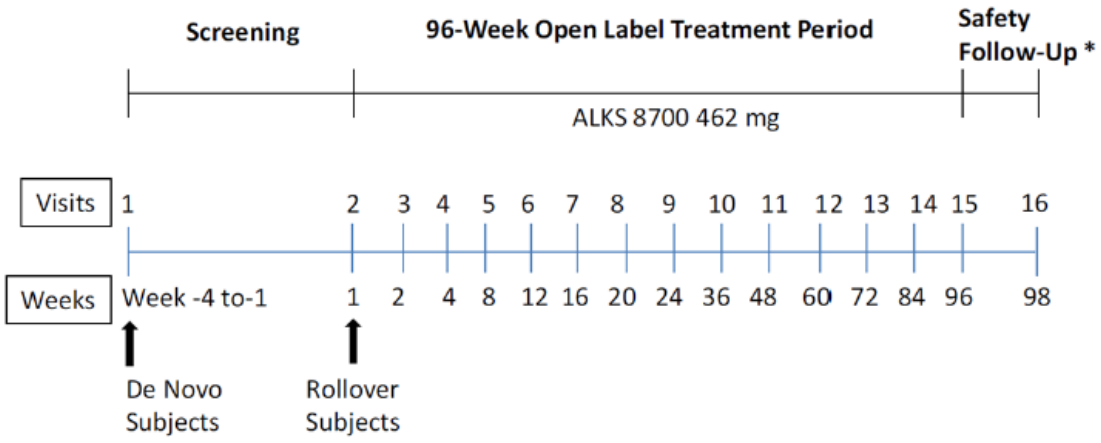
In this ongoing OL study, ALKS-8700 was administered up to 96 weeks for the treatment of RRMS.

Subjects entered the study in one of two ways:

1. De Novo Subjects: those who had not participated in any prior study of ALKS-8700.
2. Rollover Subjects: those who had completed the Treatment Period of Study ALK8700-A302.

For De Novo subjects, the study duration was up to 102 weeks, which included up to 4 weeks for screening, a 96-week open-label treatment period, and a two-week follow-up period.

Figure 4: Study A301 design schematic



* Lymphocyte monitoring follow up visits (maximum 3 visits within 6 months) may be required after this visit.

- **Study Participants (A301)**

The target population for this study was adults, aged 18 to 65 years, diagnosed with RRMS.

Approximately 1000 subjects were planned to be enrolled in this study who were to be administered ALKS-8700. A sample size of ≥ 1000 subjects meets the ICH guidance on the extent of subject exposures required to assess clinical safety for a new study drug. A total of 1057 subjects were enrolled in this study. 593 were *de novo* subjects who received ALKS-8700 and 464 were Rollover subjects from Study ALK-8700 A302 (239 subjects had previously been treated with ALKS-8700 (DRF), and 225 subjects had previously been treated with dimethyl fumarate [DMF]).

- **Treatments (A301)**

Study treatment included ALKS-8700 231 mg administered as one capsule and ALKS-8700 462 mg administered as two 231 mg capsules. At Visit 2 (Day 1), all eligible participants began open-label treatment.

Capsules were administered orally BID. Study staff administered the first dose of ALKS-8700 at Visit 2 (Day 1). From that point on during the Treatment Period, the staff dispensed ALKS-8700 for subjects' self-administration. Subjects were instructed to take study treatment with or without food. However, subjects were instructed to avoid taking study treatment with a high-fat, high-calorie meal. Detailed dosing instructions were provided to the subjects by the site personnel.

There were 18 batches of ALKS-8700 used in this study.

Table 12: Study treatment dosing schedule

Enrolment Group	**Week 1 (Days 1 to 7)**	**Week 2 onward (Day 8 onward)**
De Novo	Morning: 1 capsule of 231 mg Evening: 1 capsule of 231 mg (Total daily dose: 462 mg)	Morning: 2 capsules of 231 mg Evening: 2 capsules of 231 mg (Total daily dose: 924 mg)
Rollover	Morning: 2 capsules of 231 mg Evening: 2 capsules of 231 mg (Total daily dose: 924 mg)	

Duration of treatment and follow-up

Study duration for each subject will be approximately 102 weeks:

- 4-week screening period (*de novo* subjects only)
- 96-week treatment period
- 2-week follow-up period.

- **Objectives (A301)**

- To evaluate the long-term safety and tolerability of ALKS-8700 for up to 96 weeks of treatment in adult subjects with relapsing remitting multiple sclerosis (RRMS)
- To evaluate treatment effect over time in adult subjects with RRMS treated with ALKS-8700

- **Outcomes/endpoints (A301)**

Safety: Safety was assessed throughout the study using the following: AEs, Medical history, Physical examinations, vital sign measurements, 12-Lead ECGs, C-SSRS, Concomitant therapy and procedure recording.

Efficacy:

- Magnetic Resonance Imaging Endpoints: brain MRI scan with and without gadolinium: GdE lesion count, new/newly enlarging T2 lesion count, total T2 lesion volume, new T1 hypointense lesion count, normalised brain volume, and percent brain volume change at Weeks 48 and 96
- Clinical Efficacy Endpoints: proportion of participants with MS relapse, annualised relapse rate (ARR), progression of disability on the EDSS scores, proportion of participants experiencing progression of disability, no evidence of disease activity (NEDA), and T25FW.

- PRO: EQ-5D-5L and SF-12.

BIIB098 Concentration Assessments:

- PK samples were collected from a subset of *de novo* subjects (n = 44). The PK parameters calculated included, but were not limited to, the following: C_{max}, t_{max}, and AUC_{last}.

- **Randomisation and blinding (masking) (A301)**

There was no randomisation. This was an OL single arm study, still ongoing.

- **Statistical methods (A301)**

Complete details of the planned statistical analyses performed for this interim report are documented in the SAP, which was developed and finalised prior to database lock. An overview of analysis populations, summary strategies, and any amendments to the proposed analyses is provided in this document.

In general, summary statistics (n, mean, SD, median, minimum, and maximum for continuous variables, and number and percentage of participants in each category for categorical variables) were provided by enrolment group. All summary tables were based on observed data, and missing values were not imputed unless otherwise indicated. Measurements collected from unscheduled visits were not included in the by-visit summary tables or figures but were included in the analyses for the PCS postbaseline values and participant listings, with the exception of lymphocyte counts.

The following study populations were analysed:

- Safety population: included all enrolled subjects who received at least one dose of study drug. The Safety population was used in the safety analyses.
- Efficacy population: included data from the FAS, defined as all subjects who received at least one dose of ALKS 8700 in Study ALK-8700A301 and have had at least one post-baseline efficacy assessment of any of the efficacy endpoints, including MRI endpoints, T25-FW, EDSS, SF-12, and EQ-5D-5L. The FAS was the efficacy population and was used in the efficacy analyses.
- PK population: included a subset of subjects enrolled at selected sites who received ALKS-8700 and had at least one measurable concentration of MMF at any scheduled PK time point.

Descriptive statistics are considered acceptable due to the OL nature of the study.

Results (A301)

- **Subject disposition (A301)**

As of the data cut-off date of 02 Feb 2020, 1057 subjects entered this study: 593 were *de novo* subjects and 239 were Rollover subjects from DRF from Study A302 and 225 were Rollover subjects from DMF from Study A302. All subjects received at least one dose of study drug and were included in the Safety population. A total of 1041 subjects had at least one post-baseline efficacy assessment of any efficacy endpoint and were included in the FAS population.

- **Recruitment**

The study was to be conducted at approximately 125 sites in North America and Europe.

First subject´s first visit: 16 Dec 2015 and last subject´s last visit: N/A (study ongoing)

- **Conduct of the study**

Protocol amendments

There were two amendments that introduced no major changes. There were no changes in planned analyses from the protocol.

Protocol deviations

Major protocol deviations were reported for a total of 255 /1057 subjects as of the data cut-off date for this interim report (02 Feb 2020). According to the applicant, the protocol deviations were not considered to have a significant impact on the study results or the overall analysis of the data.

- **Baseline data (A301)**

Overall, the mean (SD) age of subjects was 42.5 (10.78) years of age, with a higher proportion of subjects being ≥ 40 years of age (59.6% [630/1057] of subjects). Overall, most of the subjects were female (72.1% [762/1057] of subjects), white (92.0% [972/1057] of subjects), and not Hispanic or Latino (96.2% [1017/1057] of subjects). A higher proportion of participants in this study were enrolled from non-US regions (57.1% [604/1057] of subjects). Mean (SD) BMI was 26.6 (6.1) kg/m2 (range 14.2 to 55.8 kg/m2).

The demographic and baseline characteristics were similar across the three groups, with the exception of the region where they were enrolled. The majority of *de novo* subjects were enrolled from non-US regions (64.9% [385/593] of subjects), while the rollover subjects were equally distributed in the two regions, with 48.1% (115/239) subjects and 51.9% (124/239) subjects enrolled in the non-US and US regions, respectively in the ALKS-8700 Rollover group, and 46.2% (104/225) of subjects and 53.8% (121/225) of subjects enrolled in the non-US and US regions, respectively in the DMF rollover group.

- **Numbers analysed (A301)**

Of the total 1057 subjects enrolled in the study, 98.5% (1041/1057) of subjects were included in the FAS population. Efficacy endpoints were considered exploratory because of the OL and single-arm design of this study. PK samples were collected in a subset of 44 *de novo* participants at selected sites. A site mistakenly took a PK sample from a subject in the ALKS-8700 Rollover group at Visit 3, and the sample was analysed with measurable MMF, so by definition, this subject was included in the PK population.

- **Outcomes and estimation (A301)**

Magnetic Resonance Imaging Endpoints (A301)

Number of GdE Lesions

At Week 96, the GdE lesion count was captured for 606 subjects (474 subjects 65 subjects, and 67 subjects in the *de novo* group, the ALKS-8700 Rollover group, and the DMF Rollover group, respectively). A mean decrease in the GdE lesion count was reported in all three groups at Week 96.

The mean (SD) change from baseline in the GdE lesions count for the *d novo* group, the ALKS-8700 Rollover group, and the DMF Rollover group was -0.85 (4.726), -0.49 (1.264), and -0.97 (2.674) lesions, respectively, which equates to 64.4%, 80.3%, and 80.2% decrease from baseline, respectively. Overall, there was an increase in the proportion of participants with 0 GdE lesions (20.7%) from baseline to Week 96 as well as decreases in the proportions of participants with 1 to 4, 5 to 8, and ≥ 9 GdE lesions (-14.7%, -3.8%, and -1.9%, respectively) from baseline to Week 96. Across the 3 groups, a high proportion of subjects (> 90%) had 0 GdE lesions at Week 96.

Number of New or Enlarging T2 lesions

New or enlarging T2 lesions from Week 48 to Week 96 were assessed for 607 subjects (475 subjects, 65 subjects, and 67 subjects in the *de novo* group, the ALKS-8700 Rollover group, and the DMF Rollover group, respectively). The mean (SD) number of new or enlarging T2 lesions that developed from Week

48 to Week 96 for the *de novo* group, the ALKS-8700 Rollover group, and the DMF Rollover group was 1.60 (6.636), 0.75 (3.881), and 0.72 (2.295) lesions, respectively.

Total T2 Lesion Volume

At Week 96, the total T2 lesion volume was evaluable for 607 subjects (475 subjects, 65 subjects, and 67 subjects in the de novo group, the ALKS-8700 Rollover group, and the DMF Rollover group, respectively). The mean (SD) percent change from baseline in total T2 lesion volume in the *de novo group*, the ALKS-8700 Rollover group, and the DMF Rollover group was 1.26% (16.4%), 0.93% (13.4%), and 0.27% (14.6%), respectively.

Number of New T1 Hypointense Lesions

The number of new T1 hypointense lesions from baseline to Week 96 was evaluable for 606 subjects (474 subjects, 65 subjects, and 67 subjects in the de novo group, the ALKS-8700 Rollover group, and the DMF Rollover group, respectively). The mean (SD) number of new T1 hypointense lesions from Week 48 to Week 96 in the *de novo* group, the ALKS-8700 Rollover group, and the DMF Rollover group was 0.83 (4.0), 0.23 (1.2), and 0.73 (5.0) lesions, respectively.

Percent Brain Volume Change (PBVC)

The PBVC from baseline to Week 96 was evaluable for 456 participants (369 subjects, 42 subjects, and 45 subjects in the de novo group, the ALKS-8700 Rollover group, and the DMF Rollover group, respectively). The mean (SD) PBVC from baseline to Week 96 in the *de novo* group, the ALKS-8700 Rollover group, and the DMF Rollover group was -0.71% (0.76%), -0.86% (0.81%), and -0.73% (0.74%), respectively, and the median PBVC value was -0.63%, -0.93%, and -0.80%, respectively, for the three groups.

Clinical Endpoints (A301)

Proportion of Participants with a Multiple Sclerosis Relapse

During the course of the study up to the interim data cutoff (07 February 2020), overall, the majority of p subjects (84.5% [893/1057]) did not experience a protocol-defined relapse during the course of the study. A total of 15.5% (164/1057) of subjects experienced between 1 and ≥ 4 protocol-defined relapses, with 12.0% (127/1057), 2.7% (29/1057), 0.6% (6/1057), and 0.2% (2/1057) of subjects experiencing 1, 2, 3, and ≥ 4 relapses, respectively.

Annualised Relapse Rate

The ARR based on protocol-defined relapses was assessed using the Safety population (N = 1057).

The ARR for the overall Safety population was 0.14, with similar ARR values across the treatment groups. The mean (SD) of ARR calculated at participant level was 0.16 (0.543).

EDSS score

The mean EDSS score calculated at baseline was similar across the groups. In the FAS population, the mean (SD) EDSS score in the *de novo* group, the ALKS 8700 Rollover group, and the DMF Rollover group was 2.71 (1.457), 2.64 (1.481), and 2.71 (1.445), respectively.

Proportion of Participants Experiencing Progression of Disability

The proportion of subjects with confirmed disability progression sustained for 12 weeks was low in all groups, with 8.1% (47/582) of subjects in the De Novo group and 7.2% (17/235) and 8.9% (20/224) participants in the ALKS-8700 and DMF Rollover groups, respectively experiencing confirmed disability progression.

No Evidence of Disease Activity

At Week 96, 663 of 1057 participants were evaluable for NEDA-3. Overall, 23.4% (155/663) of subjects achieved NEDA-3 at Week 96, with a slightly higher proportion of subjects achieving NEDA-3 at Week 96 in the *de novo group* (24.9% [121/486] of subjects) than in the Rollover groups (20.5% [18/88] of participants and 18.0% [16/89] of subjects in the ALKS-8700 Rollover group and the DMF Rollover group, respectively).

Timed 25-Foot Walk

The applicant has calculated the T25-FW scores at baseline, and these were similar across the groups. The mean (SD) values were 7.104 seconds (4.730 seconds), 6.697 seconds (4.926 seconds), and 6.635 seconds (3.618 seconds) for the *de novo group*, the ALKS-8700 Rollover group, and the DMF Rollover group, respectively.

The results, albeit from an open label and single arm study, without a comparator group can provide only a long-term view for the progress timeline of patients' condition, especially in the case of the MRI data. The efficacy data cannot be considered confirmatory, but only provide supportive data of a similar efficacy profile in comparison to what is known for DMF. External comparisons are not usually appropriate. These results should be interpreted with caution. They can, however, play the role of supportive indicators for the effect of a treatment. In such a case, the results with MS relevant efficacy measurements are in favour of an effect for DRF.

PROs followed a similar trend to that of the results of the clinical outcomes and showed stability, slowing disease activity or minor decreases in mental components as well as other quality of life components.

In the following sections, synopses of the studies, used to support the approval of Tecfidera (DMF), will be presented for completeness purposes and for convenience so that the reader does not have to look for the documents of the already approved Tecfidera (DMF).

The efficacy results from Studies 109MS301 and 109MS302 will be presented briefly separately and in an integrated manner (as compiled by the applicant), since they are considered relevant for this Marketing Authorisation procedure for DRF. More detailed efficacy information on DMF is provided in the EPAR summary for Tecfidera (EMEA/H/C/002601/0000/Rev 1).

Study 109MS301 (DEFINE)

Study 109MS301 was designed to determine the efficacy and safety of DMF in subjects with RRMS. The study was a Randomized, Multicentre, Double-Blind, Placebo-Controlled, Dose-Comparison Study. Subjects were randomised in a 1:1:1 ratio to receive DMF 240 mg BID, DMF 240 mg TID, or placebo.

Study Participants (109MS301)

1011 subjects were planned, 1237 subjects were randomised, and 1234 subjects were dosed. The intent-to-treat and safety populations comprised the 1234 randomised and dosed subjects. The MRI cohort included approximately 95% of all subjects enrolled at investigational sites whose MRI capability was validated by the MRI reading centre (540 subjects). The per-protocol population comprised subjects without major protocol violations (1090 subjects).

Summary of the Results (109MS301)

A summary of key efficacy results for Study 109MS301 is presented in Table 4. Treatment with DMF, administered as 240 mg BID or TID, significantly reduced clinical exacerbations over the 2-year treatment period, as assessed using a variety of definitions (the proportion of subjects relapsed, the time to relapse, and the ARR) as well as the risk of confirmed (12-week) disability progression at 2 years as measured by EDSS scores. As shown by Kaplan-Meier analyses of relapse and disability, the treatment effect was sustained throughout the treatment period, with the placebo and nearly overlapping DMF curves appearing to continue to diverge up to the final time point. Across a variety of subgroups defined by demographic and MS disease characteristics, DMF demonstrated a benefit on these clinical measures that was generally consistent, although a pattern of greater benefit was seen in subjects who were younger than 40 years of age, were MS treatment naïve, or had a baseline EDSS score of 2.0 or lower. A positive effect on the rate of relapses requiring intravenous steroids and of MS-related hospitalisations was also seen with DMF treatment. The effect on disability progression (EDSS) was supported by significant improvement on the multiple sclerosis functional composite score.

Significant improvement in cognition, as measured by changes in the PASAT-3 component, was also observed.

GdE and new/enlarging T2 hyperintense lesion activity was substantially and significantly suppressed by DMF treatment, with robust effects apparent as early as six months and maintained throughout the treatment period.

Statistically significant increases in magnetisation transfer ratio in normal-appearing brain tissue and in whole brain (presumably reflecting increased myelin and axonal content) were seen with both DMF doses, whereas decreased MTR was seen with placebo.

In this study, 109MS301, the estimated proportion of participants with 24-week confirmed progression at two years was 0.169 for placebo, 0.128 for BID, and 0.119 for TID (23% reduction for BID and 31% reduction for TID relative to placebo; p = 0.1893 and 0.0760, respectively).

Study 109MS302 (CONFIRM)

Study 109MS302 was a pivotal Phase 3 Randomized, Multicentre, Placebo-Controlled, double-blind, rater-blind and Active Reference (Glatiramer Acetate) Comparison Study to Evaluate the Efficacy and Safety of BG00012 in Subjects With RRMS. Subjects were randomised in a 1:1:1:1 ratio to receive DMF 240 mg BID, DMF 240 mg TID, GA, or placebo.

Study Participants (109MS302)

A total of 1232 subjects were planned, 1430 subjects were randomised, and 1417 subjects were dosed. The intent-to-treat (ITT) and safety populations comprised the 1417 randomised and dosed subjects. The MRI cohort included 681 subjects (167, 169, 170, and 175 subjects in the placebo, BG00012 BID, BG00012 TID, and GA groups, respectively) enrolled at investigational sites whose MRI capability was validated by the MRI reading centre. The per-protocol population comprised subjects without major protocol violations (1323 subjects).

Summary of the Results (109MS302)

A summary of the key efficacy results for Study 109MS302 is presented in Table 4 Treatment with DMF, administered as 240 mg BID or TID, significantly reduced clinical exacerbations over the two-year treatment period, as assessed by the ARR, the proportion of subjects relapsed, and the time to relapse.

The significant effect on the rate of relapses requiring intravenous steroid therapy and a trend toward fewer MS-related hospitalisations in the DMF groups are supportive of the beneficial clinical effects of DMF treatment in subjects with RRMS. As shown by Kaplan-Meier analyses of relapse, the treatment effect was first apparent between three to six months and was sustained throughout the two-year treatment period, with the placebo and DMF curves appearing to continue to diverge up to the final time point.

Treatment with DMF BID and TID produced clinically meaningful reductions of 21% and 24%, respectively, over placebo in 12-week confirmed disability progression. A more obvious separation was seen in the sensitivity analysis of the more rigorous 24-week confirmed disability progression, with reductions of 38% and 33% compared with placebo. While a lower than estimated proportion of participants with 12-week confirmed disability in the placebo group contributed to the lack of statistical significance for this endpoint, the change in EDSS scores lends further support for the beneficial effect of DMF treatment on disability progression.

The efficacy of DMF in reducing disability progression was also supported by improved functioning as measured by the MSFC and significant participant-reported improvement in overall physical health and functioning (SF-36 PCS) and overall impressions of general well-being (VAS).

In this study, 109MS302, the estimated proportion of subjects with 24-week confirmed progression at two years was 0.125 for placebo, 0.078 for BID, and 0.086 for TID (38% reduction for BID and 33% reduction for TID relative to placebo; p = 0.0630 and 0.1172, respectively).

Study C-1900

A phase 2, randomised, multicentre, placebo-controlled, DB, parallel-group, dose-ranging study, which provided dose-response data and supported the continued development of the DMF 240 mg TID dose. The sample size for this study was 257 randomised subjects.

Methods (C-1900)

Study C-1900 was composed of 2 parts: a 24-week, DB, placebo-controlled, safety and efficacy treatment phase (Part 1) followed by a 24-week, DB, safety extension phase (Part 2). In Part 1, subjects were randomised in a 1:1:1:1 ratio to receive one of three doses of DMF (120 mg QD, 120 mg TID, or 240 mg TID) or matching placebo for 24 weeks. In Part 2, subjects who received placebo in Part 1 switched to DMF 240 mg TID; the remaining subjects continued their same DMF dosing regimen. The primary endpoint was the total number of new GdE lesions at Weeks 12, 16, 20, and 24 (calculated as the sum of the new GdE lesions seen on the four MRI scans). Subjects who either prematurely discontinued study treatment at any time during the study or completed Part 1 but did not continue to Part 2 had a follow-up visit approximately four weeks after the last dose.

Study Participants (C-1900)

Approximately 260 subjects were planned; 257 subjects were enrolled, and 256 received at least 1 dose of study drug and were analysed.

Results (C-1900)

In this study, a dose-related effect on MRI markers of RRMS activity was observed with evidence that treatment with BG00012 (DMF) resulted in fewer inflammatory brain lesions, changes that were statistically significant in the 240 mg TID group versus placebo.

Table 13: Study C-1900 summary of key efficacy results

Endpoint	Placebo	120 mg QD	120 mg TID	240 mg TID
Primary				
Number of new GdE lesions				
Mean number (SD) Weeks 12-24	4.5 (7.4)	3.3 (5.1) p = 0.266a	3.1 (5.9) p = 0.068	1.4 (3.8) p < 0.001
Mean number (SD) Weeks 4-24	6.6 (11.4)	6.2 (8.9) p = 0.943	6.7 (10.9) p = 0.801	3.7 (11.2) p = 0.002
Secondary (listed in descending rank order)				
New or newly enlarging T2 hyperintense lesions (Mean number [SD])[a]	4.2 (5.4)	3.8 (4.7) p = 0.965	4.1 (5.7) p = 0.839	2.2 (5.4) p = 0.0006
New or newly enlarging T1 hypointense lesions (Mean number [SD]) [a]	1.7 (2.5)	1.3 (1.8) p = 0.732	1.5 (2.0) p = 0.836	0.8 (2.0) p = 0.014
ARR[b] (95% CI) Weeks 0-24	0.65 (0.43--1.01)	0.42 (0.24-0.71) p = 0.196	0.78 (0.52-1.16) p = 0.572	0.44 (0.26-0.76) p = 0.272

NOTE: All p-values compare each active treatment group versus placebo based on a Wilcoxon rank sum test; b Poisson regression model adjusted for the number of relapses in the 12 months before study entry.

Results from the pivotal Phase 3 studies 109MS301 and 109MS302 demonstrated that the dose 240 mg BID of DMF consistently provided significant improvement compared with placebo in both clinical and MRI outcome measures and showed increased efficacy compared with an approved first-line therapy, GA, in participants with RRMS. In addition, the Study 109MS303 confirmed the maintained treatment effect of DMF 240 mg BID with low relapse rates and confirmed disability progression for up to 12 years of treatment.

Based upon the similar exposure levels of MMF, after oral dosing of DRF 462 mg and DMF 240 mg, the assessment of efficacy for DRF could rely on the DMF clinical study programme.

Study 109MS303 (ENDORSE)

Study 109MS303 was the OL extension study of the pivotal Phase 3 studies (Studies 109MS301 and 109MS302) and was ongoing at the time of the submission of the Tecfidera MAA. Interim efficacy results through 03 August 2011 were provided with the Tecfidera MAA. The final results have been submitted with this MAA for DRF.

This study is currently being evaluated in a type II variation procedure for Tecfidera EMEA/H/C/002601/II/0069/G

Methods (109MS303)

This study is a multicentre, randomised, dose blind, parallel group, five-year extension study evaluating the long-term efficacy and safety of BG00012 (DMF) 240 mg BID and 240 mg TID administered orally in subjects with relapsing-remitting multiple sclerosis. A total of 2079 subjects completed the parent studies, Studies 109MS301 and 109MS302. Of these 1738 subjects (84%) were enrolled in the extension study, all of them were enrolled in the dose-blind first phase of the extension study. A total of 1736

subjects received at least one dose of study treatment. Of the 1736 subjects in Study 109MS303, approximately half (909 subjects, 52%) were treated for six years or longer.

Treatments (109MS303)

Eligible participants from Studies 109MS301 and 109MS302 were enrolled in this extension study and followed for at least 8 years. The first phase of this study was a parallel group, randomised, dose-blind, dose-comparison study, and the second phase was OL.

A total of 2079 patients completed the parent studies, Studies 109MS301 and 109MS302. Of these 1738 patients (84%) were enrolled in the extension study, all of them were enrolled in the dose-blind first phase of the extension study. A total of 1736 patients received at least 1 dose of study treatment.

Of the 1736 subjects in Study 109MS303, approximately half (909 subjects, 52%) were treated for 6 years or longer. Across all three studies, 501 subjects were continuously treated with DMF 240 mg BID and 249 subjects who were previously treated with placebo in Studies 109MS301 or 109MS302 received treatment with DMF 240 mg BID in Study 109MS303. Subjects who received treatment with DMF 240 mg BID continuously were treated for up to 12 years.

Results (109MS303)

Clinical Measures

ARR

During the overall 109MS303 study period, the majority of subjects (between 59% and 69%) had no relapses. In the first year of Study 109MS303, the adjusted ARR (95% CI) ranged from 0.125 (0.084, 0.188) to 0.183 (0.108, 0.308), and in the eighth year of Study 109MS303, it remained low and ranged from 0.077 (0.039, 0.153) to 0.129 (0.063, 0.265). There was no evidence of diminished efficacy in reduction of ARR after an additional year (a total of three years) of dosing. During the overall 109MS303 study period, the adjusted ARR (95% CI) ranged from 0.126 (0.098, 0.162) to 0.185 (0.129, 0.265). Over years 0 through 9 of Study 109MS303, the adjusted ARR (95% CI) of relapses requiring intravenous steroid treatment ranged from 0.108 (0.082, 0.143) to 0.154 (0.103, 0.229) across treatment groups. Protocol-defined objective relapses were analysed excluding data from patients after they switched to alternative MS medications. During Study 109MS303, more than half of all subjects treated with DMF 240 mg BID did not have a relapse (BID/BID, 60% and placebo/BID, 66%). 752 subjects were included in an MRI cohort. Final results in MRI assessments from this extension study showed that the majority of participants within the MRI cohort had no GdE lesions and the number of GdE lesions remained low.

The relapse rate in participants treated with DMF was low and remained steady throughout the study period (Studies 109MS301, 109MS302, and 109MS303 combined).

Figure 5 summarises the adjusted ARR for the 2 treatment groups, DMF 240 mg BID and DMF 240 mg TID by yearly interval during Studies 109MS301, 109MS302, and 109MS303. The TID group in Studies109MS301 and 109MS302 was on DMF 240 mg TID until 2014 and subsequently switched to DMF 240 mg BID.

In an integrated analysis of Studies 109MS301, 109MS302, and 109MS303, for subjects continuously treated with DMF BID/BID (n = 501; subjects treated with DMF 240 mg twice a day in Studies 109MS301 or 109MS302 and then DMF 240 mg BID in Study 109MS303), the adjusted ARR was 0.187 (95% CI, 0.156, 0.224) in Studies 109MS301 and 109MS302 and was 0.141 (95% CI, 0.119, 0.167) in Study

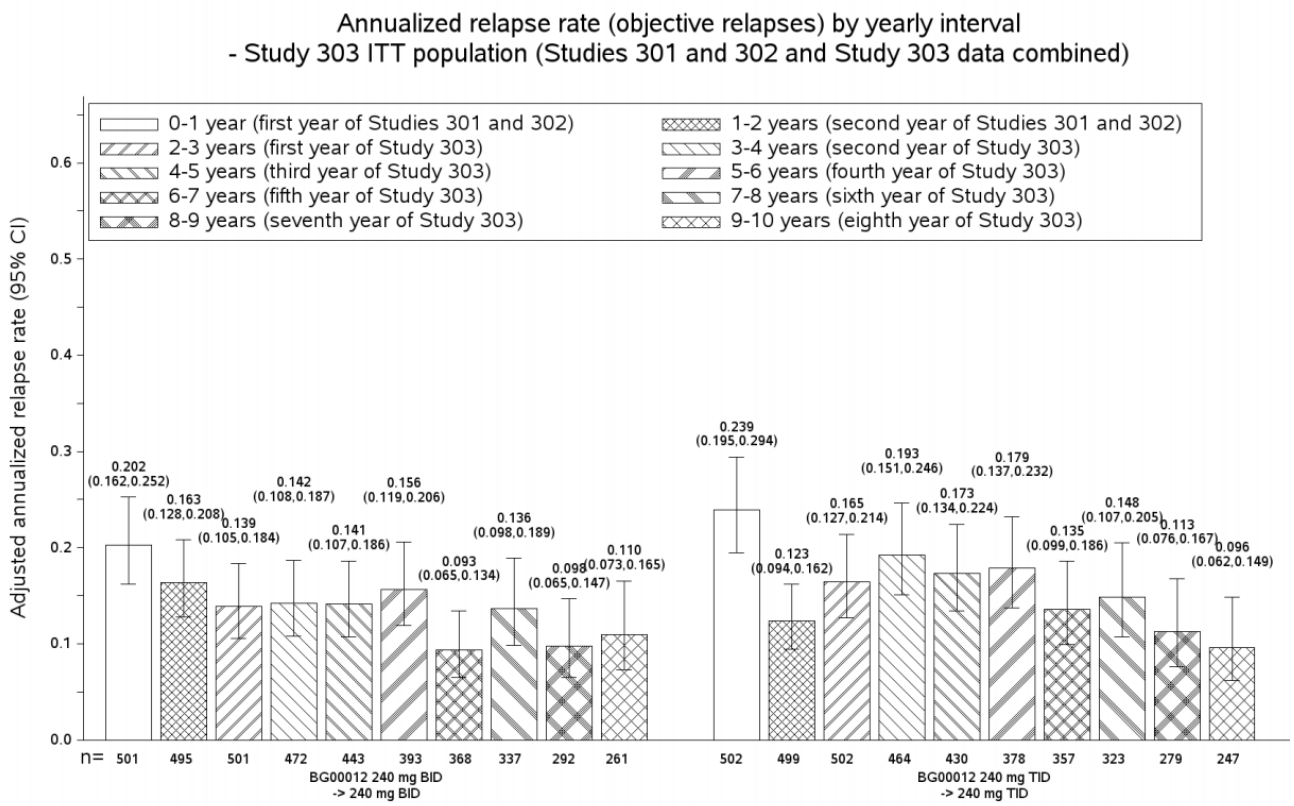
109MS303. The data in Figure 5 demonstrate that the adjusted ARR in participants treated with DMF was low and remained stable throughout the entire treatment period in Studies 109MS301 or 109MS302 and Study 109MS303 for subjects receiving BID continuously. For placebo/BID subjects (n = 249; subjects treated with placebo in Studies 109MS301 or 109MS302 and then switched to DMF 240 mg BID in Study 109MS303), adjusted ARR was 0.330 (95% CI, 0.266, 0.408) and decreased after initiation of DMF, in Study 109MS303, to 0.149 (95% CI, 0.116, 0.190), as shown in Figure 5.

Overall, the results of the updated and final long-term data of Study 109MS303 suggest maintenance of effect of DMF in adult subjects with RRMS. Efficacy findings are generally in line with the findings of the controlled parent studies as well as the preliminary results of the long-term extension study.

Efficacy data in patients who discontinued study drug can be considered sufficient to evaluate a possible rebound effect. Taking into consideration that the Study 109MS303 duration was at least eight years, the reported level of discontinuations from the extension study (56%) appears to be at an acceptable level and the reported frequency of discontinuation reasons of study treatment due to MS relapse and disease progression of around 2% is low.

Although, OL extension data should generally be interpreted with caution with regard to efficacy due to potential methodological issues, the updated and final long-term efficacy results of Study 109MS303 support the conclusion that the effect of DMF is maintained in adult patients with RRMS.

Figure 5: Annualised relapse rate (objective relapses) by year interval – Study 303 ITT population (Studies 301 and 302 and Study 303 data combined)



[1] Data after subjects switched to alternative MS medication during the period are excluded.
[2] Adjusted annualised relapse rate and 95% CI are based on negative binomial regression, except for 4-5 years, 5-6 years, 6-7 years, 7-8 years, 8-9 years, and 9-10 years (third, fourth, fifth, sixth, seventh, and eighth years of Study 303), which are based on Poisson regression, adjusted for baseline EDSS (≤2.0 vs. >2.0), baseline age (<40 vs. ≥40), region and number of relapses in the 1 year prior to 301/302 study entry.

- **Summary of main efficacy results**

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

Vumerity (DRF)

Table 14: Summary of efficacy for trial ALK8700-A302 (EVOLVE MS-2)

Title: A Phase 3 Study in Subjects with Relapsing-Remitting Multiple Sclerosis to Evaluate the Tolerability of ALKS- 8700 and Dimethyl Fumarate			
Study identifier	Protocol number: ALK-8700 A302 EudraCT number: 2017-001294-16 ClinicalTrials.gov identifier (NCT number): NCT03093324		
Design	A randomised, double-blind, multi-centre, Phase 3 study in adult subjects with RRMS conducted in two parts (Parts A and B). Parts A and B were identical in study design and included a five-week, double-blind treatment period with two treatment arms. The study had an adaptive design where data from Part A was used to modify the GI tolerability endpoints and sample size. Subjects were randomised in a 1:1 ratio to receive ALKS-8700 462 mg BID or DMF 240 mg BID and had a 1-week titration period.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		five weeks Up to four weeks Patients could enrol in study ALK-8700 A301
Hypothesis	Superiority		
Treatments groups	ALKS-8700		ALKS-8700 462 mg BID for five weeks (with one-week titration at 231 mg BID); 254 randomised (60 in Part A and 194 in Part B).
	DMF		DMF 240 mg BID for five weeks (with one-week titration at 120 mg BID); 252 randomised (60 in Part A and 192 in Part B).
Endpoints and definitions	Primary endpoint Number of days with any IGISIS score ≥2 in Parts A and B	IGISIS (Parts A+B)	Number of days with any Individual GI Symptom and Impact Scale (IGISIS) individual symptom intensity score ≥ 2 Relative to Exposure Days in Parts A and B.
	Secondary: Number of days with any IGISIS score ≥ 2 in Part B	IGISIS (Part B)	Number of days with any IGISIS individual symptom intensity score ≥ 2 relative to exposure days in Part B.
	Secondary: Number of days with any IGISIS score ≥ 1 in Parts A and B	IGISIS ≥ 1 (Parts A+B)	Number of days with any IGISIS individual symptom intensity score ≥ 1 relative to exposure days in Parts A and B.
	Secondary: Number of days with any IGISIS score ≥ 3 in Parts A and B	IGISIS ≥ 3 (Parts A+B)	Number of days with any IGISIS individual symptom intensity score ≥ 3 relative to exposure days in Parts A and B.
	Secondary: Number of days with any GGISIS symptom intensity score ≥ 1 in Parts A and B	GGISIS ≥ 1 (Parts A+B)	Number of days with a (Global GI Symptom and Impact Scale) GGISIS symptom intensity score ≥ 1 relative to exposure days in Parts A and B.

	Secondary: Number of days with any GGISIS symptom intensity score ≥ 2 in Parts A and B	GGISIS ≥2 (Parts A+B)	Number of days with a GGISIS symptom intensity score ≥ 2 relative to exposure days in Parts A and B.
	Secondary: Number of days with any GGISIS symptom intensity score ≥ 3 in Parts A and B	GGISIS ≥3 (Parts A+B)	Number of days with a GGISIS symptom intensity score ≥ 3 relative to exposure days in Parts A and B.
	Secondary: Worst IGISIS score by week during the five-week Treatment Period in Parts A and B	Worst IGISIS (Parts A+B)	Worst IGISIS individual symptom intensity score by week during the five-week Treatment Period in Parts A and B. This table provides the worst IGISIS during treatment period, see Notes section for the 'by week' data.

Database lock	25 July 2019		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Full Analysis Set (FAS) The FAS included all enrolled subjects who received at least one dose of study drug and completed at least one post-baseline GI tolerability assessment (GGISIS or IGISIS). Time point: Week 5		
Descriptive statistics and estimate variability	Treatment group	ALKS 8700	DMF
	Number of subjects	253	249
	Primary: Number of days with any IGISIS ≥ 2 (Parts A+B) mean SD Min, Max	 1.5 2.85 0, 19	 2.5 4.68 0, 34
	Secondary: Number of days with any IGISIS ≥ 2 (Part B) mean SD Min, Max	 1.3 2.70 0, 19	 2.2 4.22 0, 34
	Secondary: Number of days with any IGISIS ≥ 1 (Parts A+B) mean SD Min, Max	 2.9 4.46 0, 26	 3.9 5.84 0, 37
	Secondary: Number of days with any IGISIS ≥ 3 (Parts A+B) mean SD Min, Max	 0.9 2.25 0, 19	 1.5 3.85 0, 30
	Secondary: Number of days with any GGISIS ≥ 1 (Parts A+B) mean SD Min, Max	 2.1 4.43 0, 35	 2.8 5.19 0, 34
	Secondary:		

	Number of days with any GGISIS ≥ 2 (Parts A+B) mean SD Min, Max		 1.1 3.25 0, 28	 1.5 3.53 0, 27
	Secondary: Number of days with any GGISIS ≥ 3 (Parts A+B) mean SD Min, Max		 0.7 2.26 0, 20	 0.9 2.57 0, 25
	Secondary: Worst IGISIS during treatment period mean SD Min, Max		 1.9 2.31 0, 10	 2.3 2.0 0, 10
Effect estimate per comparison	**Primary:** Number of days with any IGISIS ≥ 2 (Parts A+B)	Comparison groups	ALKS-8700 vs DMF
		Reduction vs DMF (Rate ratio)	45.8% 0.542
		95% confidence interval	(0.390, 0.754)
		P-value	0.0003
	Secondary: Number of days with any IGISIS ≥ 2 (Part B)	Comparison groups	ALKS 8700 vs DMF
		Reduction vs DMF (Rate ratio)	48.0% 0.520
		95% confidence interval	(0.356, 0.760)
		P-value	0.0007
	Secondary: Number of days with any IGISIS ≥ 1 (Parts A+B)	Comparison groups	ALKS-8700 vs. dimethyl fumarate
		Reduction vs. dimethyl fumarate (Rate ratio)	28.6% 0.714
		95% confidence interval	(0.554, 0.921)
		P-value	0.009
	Secondary: Number of days with any IGISIS ≥ 3 (Parts A+B)	Comparison groups	ALKS-8700 vs. dimethyl fumarate
		Reduction vs. dimethyl fumarate (Rate ratio)	44.5% 0.555
		95% confidence interval	(0.357, 0.862)
		P-value	0.009
	Secondary: Number of days with any GGISIS ≥ 1 (Parts A+B)	Comparison groups	ALKS-8700 vs. dimethyl fumarate
		Reduction vs DMF (Rate ratio)	30.4% 0.696
		95% confidence interval	(0.499, 0.972)
		P-value	0.033
	Secondary:	Comparison groups	ALKS-8700 vs. dimethyl fumarate
		Reduction vs. dimethyl fumarate	33.8%

	Number of days with any GGISIS ≥ 2 (Parts A+B)	(Rate ratio)	0.662
		95% confidence interval	(0.425, 1.031)
		P-value	0.068
	Secondary: Number of days with any GGISIS ≥ 3 (Parts A+B)	Comparison groups	ALKS-8700 vs. dimethyl fumarate
		Reduction vs DMF (Rate ratio)	28.7% 0.713
		95% confidence interval	(0.417, 1.217)
		P-value	0.215
	Secondary: Worst IGISIS during treatment period	Comparison groups	ALKS-8700 vs. dimethyl fumarate
		Reduction vs DMF (LSMD)	-0.4
		Standard error 95% confidence interval	0.21 (-0.8, 0.0)
		P-value	0.069
Notes	For more information about the Worst IGISIS individual symptom intensity score by week during the five-week treatment period in Parts A and B, refer to CSR Section 11.2.2.4, where the 'by week' data is presented in Figures 3 to 8.		

Table 15: Summary of efficacy for trial ALK-8700 A301 (EVOLVE MS-1)

Title: A Phase 3 Open Label Study to Evaluate the Long-term Safety and Tolerability of ALKS-8700 in Adults with Relapsing Remitting Multiple Sclerosis		
Study identifier	Protocol number: ALK-8700 A301 EudraCT number: 2015-005160-41 ClinicalTrials.gov identifier (NCT number): NCT02634307	
Design	A Phase 3 multicentre open-label study to evaluate the long-term safety and tolerability of ALKS-8700 in adults for the treatment of RRMS. subjects were either: • De Novo: had not participated in any prior study of ALKS-8700. • Rollover: had completed the treatment period of study ALK-8700 A302. The De Novo subjects initiated treatment with ALK-8700 231 mg BID for one week and then received ALK-8700 432 mg BID for the remainder of the study. Rollover patients received ALK8700 462 mg BID for 96 weeks.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	96 weeks 4 weeks (only applicable to *de novo* patients) not applicable
Hypothesis	Not applicable (see 'Notes' section below)	
Treatments groups	De Novo	ALKS-8700 231mg BID Day 1 to Day 7. ALKS 8700 462 mg BID Day 8 until week 96; subjects enrolled: 593.
	Rollover ALKS-8700	ALKS-8700 462 mg BID for 96 weeks; subjects enrolled: 239.
	Rollover DMF	ALKS-8700 462 mg BID for 96 weeks; subjects enrolled: 225.

Endpoints and definitions	Number of GdE lesions	GdE Lesions	MRI endpoint: Number of gadolinium-enhancing lesions and change from baseline	
	Number of new or enlarging T2 lesions	T2 lesions	MRI endpoint: Number of new or enlarging T2 lesions since previous assessment	
	Total T2 lesion volume	T2 volume	MRI endpoint: Total T2 lesion volume (cc) and percent change from baseline.	
	Number of new T1 hypointense lesion	T1 lesions	MRI endpoint: The number of new unenhanced T1 hypointense lesions since previous assessment.	
	Percent brain volume change (PBVC)	% Brain volume change	MRI endpoint: PBVC from baseline.	
	Annualised relapse rate	ARR	Clinical endpoint: The ARR based on protocol -defined relapses was assessed using the Safety population (N = 1057).	
	EDSS score	EDSS	Clinical endpoint: change from baseline in EDSS score.	
	Disability Progression measured by EDSS	% Subjects with 12-week confirmed disability progression	Clinical endpoint: Proportion of participants experiencing progression of disability measured by EDSS that was sustained for 12 weeks.	
	No evidence of disease activity (NEDA-3)	NEDA-3	Clinical endpoint (assessed using the Safety population): NEDA-3 is a composite of 3 measures of disease activity: no relapses, no confirmed disability progression sustained for 12 weeks as measured on EDSS, no MRI activity (i.e., no new or enlarging T2 lesions or GdE lesions). Proportion of subjects with NEDA-3.	
	No evidence of disease activity (NEDA-4)	NEDA-4	Clinical endpoint (assessed using the Safety population): NEDA-4 was the defined as NEDA-3 with the addition of a mean annualised rate of brain volume loss of less than 0.4%. Proportion of subjects with NEDA-4.	
	Timed 25-foot walk	T25-FW	Clinical endpoint: The T25-FW score was assessed using the FAS population at baseline and every 12 weeks thereafter up to Week 96 to evaluate the quantitative mobility and leg functioning of participants during the course of study. Change in 25-Foot Walk from baseline.	
Database lock	07 February 2020			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	All efficacy analyses were carried out using the full analysis set (FAS) population, with the exception of Relapse, which was summarised using the Safety population. Time point: Week 48 and Week 96			
Descriptive statistics and estimate variability	Treatment group	*De Novo*	Rollover ALKS 8700	Rollover DMF
	Number of subjects (the number of subjects at Week 48 and 96 varies and	582	235	224

therefore is included (n) in each row)			
GdE Lesions at week 48 n mean (SD)	522 0.25 (1.534)	158 0.16 (1.062)	157 0.06 (0.334)
GdE Lesions change from baseline to Week 48 n mean (SD)	522 -1.04 (3.992)	157 -0.46 (1.869)	157 -0.79 (2.051)
GdE Lesions at week 96 n mean (SD)	474 0.47 (3.816)	65 0.12 (0.484)	67 0.24 (0.939)
GdE Lesions change from baseline to Week 96 n mean (SD)	474 -0.85 (4.726)	65 -0.49 (1.264)	67 -0.97 (2.674)
New or Enlarging T2 lesions from baseline to week 48 n mean (SD)	522 2.72 (7.535)	158 0.87 (2.647)	157 0.90 (2.211)
New or Enlarging T2 lesions from week 48 to week 96 n mean (SD)	475 1.60 (6.636)	65 0.75 (3.881)	67 0.72 (2.295)
Total T2 lesion volume at week 48 n mean (SD)	522 13.80 (13.963)	158 13.41 (14.339)	157 12.00 (13.600)
Total T2 volume percent change from baseline to Week 48 n mean (SD)	522 0.48 (14.070)	158 0.58 (14.617)	157 1.48 (20.485)
Total T2 lesion volume at week 96 n mean (SD)	475 14.04 (14.234)	65 13.37 (15.337)	67 14.19 (17.940)
Total T2 volume percent change from baseline to Week 96 n mean (SD)	475 1.26 (16.358)	65 0.93 (13.375)	67 0.27 (14.598)
New T1 Hypointense lesions from baseline to week 48 n mean (SD)	522 1.92 (5.026)	157 0.62 (1.595)	157 0.57 (1.156)
New T1 Hypointense lesions from week 48 to week 96 n mean (SD)	474 0.83 (3.966)	65 0.23 (1.183)	67 0.73 (4.947)

% Brain volume change from baseline to week 48 n mean (SD)	 483 -0.38 (0.634)	 134 -0.46 (0.545)	 137 -0.39 (0.599)
% Brain volume change from baseline to week 96 n mean (SD)	 369 -0.71 (0.760)	 42 -0.86 (0.811)	 45 -0.73 (0.735)
ARR (Safety population) n unadjusted ARR	 593 0.14	 239 0.13	 225 0.13
EDSS at week 48 n mean (SD)	 521 2.78 (1.512)	 160 2.68 (1.555)	 159 2.72 (1.517)
EDSS change from baseline to Week 48 n mean (SD)	 521 0.03 (0.614)	 160 0.01 (0.555)	 159 0.00 (0.683)
EDSS at week 96 n mean (SD)	 478 2.77 (1.491)	 64 2.82 (1.796)	 64 2.91 (1.825)
EDSS change from baseline to Week 96 n mean (SD)	 478 0.07 (0.631)	 64 0.02 (0.784)	 64 0.11 (0.704)
% Subjects with 12-week confirmed disability progression n (%)	 582 (8.1)	 235 (7.2)	 224 (8.9)
NEDA-3 Number of evaluable patients at week 48 Number meeting NEDA-3 criteria (%)	 525 223 (42.5)	 164 89 (54.3)	 161 86 (53.4)
NEDA-3 Number of evaluable patients at week 96 Number meeting NEDA-3 criteria (%)	 486 121 (24.9)	 88 18 (20.5)	 89 16 (18.0)
NEDA-4 Number of evaluable patients at week 48 Number meeting NEDA-4 criteria (%)	 504 123 (24.4)	 153 38 (24.8)	 151 42 (27.8)
NEDA-4 Number of evaluable patients at week 96 Number meeting NEDA-4 criteria (%)	 419 60 (14.3)	 71 4 (5.6)	 75 4 (5.3)
T25-FW at week 48 n mean (SD)	 517 7.287 (6.702)	 156 6.758 (5.112)	 159 6.816 (4.676)
T25-FW change from baseline at Week 48 n mean (SD)	 517 0.135 (3.782)	 156 -0.054 (2.328)	 159 0.272 (2.702)
T25-FW at week 96			

	n mean (SD)	476 6.975 (4.563)	62 5.870 (2.042)	63 6.799 (3.722)
	T25-FW change from baseline at Week 96 n mean (SD)	 476 -0.043 (2.582)	 62 -0.178 (1.198)	 63 0.822 (2.693)
Notes	ALK-8700 A301 is an open label single arm long-term safety study, where efficacy endpoints are collected as exploratory. No comparisons or hypotheses were planned or conducted. The data cut used was 7 February 2020. An additional interim CSR was submitted during the review of the MAA with a data cut of 01 September 2020.			
Analysis description	Exploratory			

Tecfidera (DMF)

Table 16: Summary of efficacy for trial 109MS301 (DEFINE)

Title: A Randomized, Multicentre, Double-Blind, Placebo-Controlled, Dose-Comparison Study to Determine the Efficacy and Safety of BG00012 (DMF) in Subjects with Relapsing-Remitting Multiple Sclerosis			
Study identifier	Protocol number: 109MS301 EudraCT number: 2006-003696-12 ClinicalTrials.gov identifier (NCT number): NCT00420212		
Design	A randomised, multicentre, double-blind, placebo-controlled, dose-comparison study in subjects with relapsing-remitting multiple sclerosis (RRMS). Subjects were randomised in a 1:1:1 ratio to receive placebo, BG00012 (DMF) 240 mg BID, or BG00012(DMF) 240 mg TID.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		96 weeks Not applicable Not applicable (separate extension Study 109MS303)
Hypothesis	Superiority		
Treatments groups	BG0012 240 mg BID (BG0012 BID)		BG00012 taken orally 240 mg twice daily (BID) (2 capsules [120 mg each] BID and 2 placebo capsules four times a day) (after a starting dose of 1 BG00012 capsule twice a day and 1 placebo capsule once a day for 7 days). Treatment duration: 96 weeks treatment Randomised: N= 411(and 410 dosed).
	BG0012 240 mg TID (BG0012 TID)		BG00012 taken orally 240 mg TID (2 capsules [120 mg each] TID) (after a starting dose of 1 BG00012 capsule 3 times a day for 7 days). Treatment duration: 96 weeks treatment Randomised: N = 416 (and 416 dosed).
	Placebo		Placebo taken orally (2 capsules TID). Treatment duration: 96 weeks treatment Randomised: N = 140 (and 408 dosed).
Endpoints and definitions	**Primary:** Proportion of subjects relapsed at 2 years	Proportion of subjects with relapse	Proportion of subjects who experienced a protocol-defined relapse at 2 years. Relapse assessment was evaluated at the site by a blinded treating neurologist based on findings from an examining neurologist who was also blinded. Relapses that were determined to meet objective, protocol-defined criteria were subsequently evaluated by an independent committee of neurologists (INEC). The proportion of subjects relapsed is estimated from the Kaplan-Meier curve of the time to the first relapse. Hazard ratios, percent

			reductions (with 95% CIs) and P-values are from the Cox proportional hazards model for time to the first relapse, adjusted for baseline EDSS (<=2.0 vs. >2.0), baseline age (<40 vs >=40), region and number of relapses in the one year prior to study entry.
	Secondary: Total Number of New or Newly Enlarging T2 Hyperintense Lesions at 2 Years	New/ enlarging T2 lesions	Number of new or newly enlarging T2 hyperintense lesions measured by MRI. Adjusted mean number of new/enlarging T2 lesions, lesion mean ratio, percent change (with 95% CIs) and P-values are from the negative binomial regression model, adjusted for region and baseline volume of T2 lesions.
	Secondary: Number of Gd-Enhancing Lesions at 2 Years	Gd+ lesions	Number of Gd-enhancing lesions measured by MRI. Odds ratios and P-values are from the ordinal logistic regression, adjusted for region and baseline number of gf Gd+ lesions.
	Secondary: Annualised Relapse Rate at 2 Years	ARR	Number of protocol-defined relapses per year over 2 years, confirmed by the blinded INEC. The endpoint was analysed using a negative binomial regression model adjusted for baseline EDSS score (≤2.0 versus>2.0), baseline age (<40 versus ≥40 years), region, and the number of relapses in the year prior to study entry. The logarithmic transformation of the time on study was included in the model as the "offset" parameter.
	Secondary: Time to confirmed (12-week) disability progression as measured by EDSS	Confirmed disability progression (12-week)	Confirmed disability progression was defined as at least a 1.0 point increase on the Expanded Disability Status Scale from baseline EDSS ≥ 1.0 that was sustained for 12 weeks, or at least a 1.5 point increase on the EDSS from baseline EDSS = 0 that was sustained for 12 weeks. A progression could start but could not be confirmed when a subject was experiencing an INEC-confirmed relapse. The proportion of subjects progressed at 2 years is estimated from the Kaplan-Meier curve of time to progression. Hazard ratios, percent reductions (with 95% CIs) and P-values are from the Cox proportional hazards model for time to progression, adjusted for baseline EDSS, region and baseline age (<40 vs >=40).
	Secondary: Time to confirmed (24-week) disability progression as measured by EDSS	Confirmed disability progression (24-week)	Confirmed disability progression was defined as at least a 1.0 point increase on the Expanded Disability Status Scale from baseline EDSS ≥ 1.0 that was sustained for 24 weeks, or at least a 1.5 point increase on the EDSS from baseline EDSS = 0 that was sustained for 24 weeks. A progression could start but could not be confirmed when a subject was experiencing an INEC-confirmed relapse. The proportion of subjects progressed at 2 years is estimated from the Kaplan-Meier curve of time to progression. Hazard ratios, percent reductions (with 95% CIs) and P-values are from the Cox proportional hazards model for time to progression, adjusted for baseline EDSS, region and baseline age (< 40 vs. >=40).
Database lock	01 April 2011		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat Time point: Week 96		

Descriptive statistics and estimate variability	Treatment group	BG0012 BID	BG0012 TID	Placebo
	Number of subjects	410	416	408
	Primary: Proportion of subjects with relapse[1]	0.270	0.260	0.461
	Hazard ratio[2] 95% confidence interval	0.51 (0.40, 0.66)	0.50 (0.39, 0.65)	-
	Secondary: New/enlarging T2 lesions (mean)	3.2	4.9	16.5
	Adjusted mean[3]	2.6	4.4	17.0
	Median	1.0	1.0	7.0
	Secondary: Gd lesions (mean)	0.1	0.5	1.8
	Median	0	0	0
	Secondary: ARR (adjusted)[3]	0.172	0.189	0.364
	95% confidence interval	(0.138, 0.214)	(0.153, 0.234)	(0.303, 0.436)
	Secondary: Proportion with confirmed (12- week) disability progression[1]	16.4%	17.7%	27.1%

Effect estimate per comparison	**Primary:** Relapse	Comparison groups	BG0012 BID	BG0012 TID
		Reduction versus placebo	49%	50%
		Hazard ratio[2] 95% confidence interval	0.51 (0.40, 0.66)	0.50 (0.39, 0.65)
		P-value	<0.0001	<0.0001
	Secondary: New/enlarging T2 lesions	Comparison groups	BG0012 BID	BG0012 TID
		Reduction versus placebo	85%	74%
		95% confidence interval	(-90, -77)	(-83, -62)
		P-value	< 0.0001	< 0.0001
	Secondary: Gd+ lesions	Comparison groups	BG0012 BID	BG0012 TID
		Reduction versus placebo	90%	73%
		Odds ratio[4] 95% confidence interval	0.10 (0.05, 0.22)	0.27 (0.15, 0.46)
		P-value	<0.0001	<0.0001
	Secondary: ARR	Comparison groups	BG0012 BID	BG0012 TID
		Reduction versus placebo	53%	48%
		Rate ratio[3] 95% confidence interval	0.473 (0.365, 0.613)	0.521 (0.404, 0.670)
		P-value	<0.0001	<0.0001

	Secondary: Time to confirmed (12- week) disability progression	Comparison groups	BG0012 BID	BG0012 TID
		Reduction versus placebo	38%	34%
		Hazard ratio[2] 95% confidence interval	0.62 (0.44, 0.87)	0.66 (0.48, 0.92)
		P-value	0.0050	0.0128
Notes	[1]Kaplan-Meier estimate, [2]based on Cox proportional hazards model, [3]based on negative binomial regression, [4]based on ordinal logistic regression.			
Analysis description	**Sensitivity analysis**			
Analysis population and time point description	Intent to treat (for clinical endpoints) at 96 weeks			
Descriptive statistics and estimate variability	**Treatment group**	**BG0012 BID**	**BG0012 TID**	**Placebo**
	Number of subjects	410	416	408
	Proportion with confirmed (24-week) disability progression[1]	12.8%	11.9%	16.9%

Effect estimate per comparison	Time to confirmed (24-week) disability progression	Comparison groups	BG0012 BID	BG0012 TID
		Hazard ratio[2]	0.77	0.69
		95% confidence interval[2]	(0.52, 1.14)	(0.46, 1.04)
		Percent reduction versus placebo[2]	23%	31%
		P-value[2]	0.1893	0.0760
[1]Based on Kaplan-Meier product limit method, [2]based on Cox proportion hazards model.				

Table 17: Summary of efficacy for trial 109MS302 (CONFIRM)

Title: A Randomized, Multicentre, Placebo-Controlled and Active Reference (Glatiramer Acetate) Comparison Study to Evaluate the Efficacy and Safety of BG00012 (DMF) in Subjects With Relapsing-Remitting Multiple Sclerosis		
Study identifier	Protocol number: 109MS302 EudraCT number: 2006-003697-10 ClinicalTrials.gov identifier (NCT number): NCT00451451	
Design	A Phase 3, randomised, multicentre, parallel-group, placebo-controlled and active reference (GA) comparator, double-blind (only for BG00012/placebo), rater-blind study. Subjects were randomised in a 1:1:1:1 ratio to receive BG00012 240 mg BID, BG00012 240 mg TID, placebo or glatiramer acetate.	
	Duration of main phase:	96 weeks (additional 4 weeks follow up for subjects who do not enrol into the extension Study, 109MS303)
	Duration of Run-in phase:	Not applicable
	Duration of Extension phase:	Not applicable (separate extension Study 109MS303)
Hypothesis	Superiority (for each active treatment group versus placebo)	

Treatments groups	BG0012 240 mg BID (BG0012 BID)		BG00012 240 mg taken orally twice daily (2 capsules [120 mg each] BID and 2 placebo capsules QD) (after a starting dose of 1 BG00012 capsule twice and 1 placebo capsule QD a day for 7 days). Treatment duration: 96 weeks Randomised: N = 362 (and 359 dosed).
	BG0012 240 mg TID (BG0012 TID)		BG00012 240 mg taken orally TID (2 capsules [120 mg each] TID) (after a starting dose of 1 BG00012 capsule TID for 7 days). Treatment duration: 96 weeks treatment Randomised: N = 345 (and dosed).
	Placebo		Placebo taken orally (2 capsules TID) (after a starting dose of 1 matching placebo capsule 3 times a day for 7 days). Treatment duration: 96 weeks treatment
	Glatiramer acetate (GA)		GA (20 mg subcutaneous [SC] injection, QD). Treatment duration: 96 weeks Randomised: N = 360 (and 350 dosed).
Endpoints and definitions	**Primary:** Annualised relapse rate at 2 years	ARR	Number of protocol-defined relapses per year over 2 years, confirmed by the blinded INEC. The endpoint was analysed using a negative binomial regression model adjusted for baseline EDSS score (≤ 2.0 vs.> 2.0), baseline age (< 40 versus ≥ 40 years), region, and the number of relapses in the year prior to study entry. The logarithmic transformation of the time on study was included in the model as the "offset" parameter.
	Secondary: Total Number of new or newly enlarging T2 hyperintense lesions at 2 years	T2 lesions	Number of new or newly enlarging T2 hyperintense lesions measured by MRI. Adjusted mean number of new/enlarging T2 lesions, lesion mean ratio, percent change (with 95% CIs) and P-values are from the negative binomial regression model, adjusted for region and baseline volume of T2 lesions.
	Secondary: Number of new T1 hypointense lesions at 2 years	T1 lesions	Number of new T1 hyperintense lesions measured by MRI. Adjusted mean number of new T1 lesions, lesion mean ratio, percent reduction (with 95% CIs) and P-values are from the negative binomial regression model, adjusted for region and baseline volume of T1 lesions.
	Secondary: Proportion of subjects with clinical relapse at 2 Years	Proportion with clinical relapse	Proportion of subjects with clinical relapses at 96 weeks (2 years) confirmed by the INEC. The proportion of subjects relapsed is estimated from the Kaplan-Meier curve of the time to the first relapse. Hazard ratios, percent reductions (with 95% CIs) and P-values are from the Cox proportional hazards model for time to the first relapse, adjusted for baseline EDSS (<=2.0 vs. >2.0), baseline age (< 40 vs. ≥40), region and number of relapses in the one year prior to study entry.
	Secondary: Time to confirmed (12-week) disability progression as measured by EDSS	Confirmed disability progression (12-week)	Confirmed disability progression was defined as at least a 1.0 point increase on the EDSS from baseline EDSS 1.0 that was sustained for 12 weeks, or at least a 1.5 point increase on the EDSS from baseline EDSS = 0 that was sustained for 12 weeks. A progression could start but could not be confirmed when a subject was experiencing an INEC-confirmed relapse. The proportion of subjects progressed at 2 years is estimated from the Kaplan-Meier curve of time to progression. Hazard ratios, percent reductions (with 95% CIs) and P-values are from the Cox proportional hazards model for

			time to progression, adjusted for baseline EDSS, region and baseline age (< 40 vs ≥40).
	Secondary: Time to confirmed (24-week) disability progression as measured by EDSS	Confirmed disability progression (24-week)	Confirmed disability progression was defined as at least a 1.0 point increase on the EDSS from baseline EDSS 1.0 that was sustained for 24 weeks, or at least a 1.5 point increase on the EDSS from baseline EDSS = 0 that was sustained for 24 weeks. A progression could start but could not be confirmed when a subject was experiencing an INEC-confirmed relapse. The proportion of subjects progressed at 2 years is estimated from the Kaplan-Meier curve of time to progression. Hazard ratios, percent reductions (with 95% CIs) and P-values are from the Cox proportional hazards model for time to progression, adjusted for baseline EDSS, region and baseline age (< 40 vs ≥ 40).
Database lock	6 October 2011		

Results and Analysis

Analysis description	**Primary Analysis**				
Analysis population and time point description	Intent to treat Time point: Week 96				
Descriptive statistics and estimate variability	Treatment group	BG0012 BID	BG0012 TID	Placebo	GA
	Number of subjects	359	345	363	350
	ARR (adjusted)[1]	0.224	0.198	0.401	0.286
	95% confidence interval	(0.179, 0.282)	(0.156, 0.252)	(0.329, 0.488)	(0.232, 0.353)
	New/enlarging T2 lesions (mean)	5.7	5.1	19.9	9.6
	Adjusted mean[1] 95% confidence interval	5.1 (3.9, 6.6)	4.7 (3.6, 6.2)	17.4 (13.5,22.4)	8.0 (6.3,10.2)
	median	2.0	2.0	11.0	3
	New T1 hypointense lesions (mean)	3.8	2.7	8.1	4.5
	median	1.0	1.0	4.0	2.0
	Proportion with clinical relapse[2]	29.1%	24.1%	41.0%	32.1%

	Hazard ratio[3] active/placebo 95% confidence interval	0.66 (0.51, 0.86)	0.55 (0.42, 0.73)	-	0.71 (0.55, 0.92)	
	Proportion with confirmed (12-week) disability progression[2]	12.8%	13.0%	16.9%	15.6%	
Effect estimate per comparison	**Primary:** ARR	Comparison groups		BG0012 BID	BG0012 TID	GA
		Reduction versus placebo[1]		44.0%	50.5%	28.6%
		95% confidence interval		(26.0, 57.7)	(33.8, 63.1)	(6.9, 45.2)
		P-value		<0.0001	<0.0001	0.0128
	Secondary: New/enlarging T2 lesions	Comparison groups		BG0012 BID	BG0012 TID	GA
		Reduction versus placebo		71%	73%	54%
		95% confidence interval		(59, 79)	(62, 80)	(37, 67)
		P-value		<0.0001	<0.0001	<0.0001
	Secondary: T1 hypointense lesions	Comparison groups		BG0012 BID	BG0012 TID	GA
		Reduction versus placebo		57%	65%	41%
		95% confidence interval		(39, 70)	(51, 76)	(18, 58)
		P-value		<0.0001	<0.0001	0.0021
	Secondary: Proportion with clinical relapse	Comparison groups		BG0012 BID	BG0012 TID	GA
		Reduction versus placebo		34.0%	44.6%	28.6%
		95% confidence interval		(14.1, 49.3)	(26.6, 58.1)	(7.8, 44.6)
		P-value		0.0020	<0.0001	0.0097
	Secondary: Time to confirmed (12-week) disability progression	Comparison groups		BG0012 BID	BG0012 TID	GA
		Reduction versus placebo[3]		21.4%	23.8%	7.3%
		Hazard ratio[3] 95% confidence interval[3]		0.79 (0.52, 1.19)	0.76 (0.50, 1.16)	0.93 (0.63, 1.37)
		P-value[3]		0.2536	0.2041	0.7036
Notes	[1]Based on negative binomial regression, [2]based on Kaplan-Meier estimate, [3]based on Cox proportion hazards model. Statistical testing was performed for each active treatment group relative to placebo.					

Analysis description	**Sensitivity Analysis**				
Analysis population and time point description	Intent to treat (for clinical endpoints) at 96 weeks				
Descriptive statistics and estimate variability	Treatment group	BG0012 BID	BG0012 TID	Placebo	GA
	Number of subjects	359	345	363	350
	Proportion with confirmed (24-week) disability progression[1]	0.078	0.086	0.125	0.108
Effect estimate per comparison	Time to confirmed (24- week) disability progression	Comparison groups	BG0012 BID	BG0012 TID	GA
		Percent reduction versus placebo[2]	38.3	33.1	13
		Hazard ratio[2]	0.62	0.67	0.87
		95% confidence interval[2]	(0.37, 1.03)	(0.40, 1.11)	(0.55, 1.38)
		P-value[2]	0.0630	0.1172	0.5528
[1]Based on Kaplan-Meier product limit method, [2]based on Cox proportion hazards model.					

2.6.5.3. Clinical studies in special populations

No comparisons or analyses were performed to compare the efficacy of DRF in different subpopulations.

Paediatric population

The efficacy of DMF has not yet been established in paediatric subjects.

Study 109MS202

DMF was evaluated in a prospective open-label, uncontrolled Study 109MS202 (FOCUS) in 22 paediatric subjects with RRMS aged 13 to 17 years (4 subjects ≤ 14 years). Subjects received DMF 120 mg BID for 7 days followed by DMF 240 mg BID for 24 weeks.

Study 109MS311

This study was a multicentre, open-label, extension study to determine the long-term safety and efficacy of DMF in paediatric subjects with RRMS. Subjects from Study 109MS202 subsequently entered an extension Study 109MS311 (CONNECTED) for a further 96 weeks.

Study 109MS306

The safety and efficacy of DMF in children aged 10 to ≤ 18 years is being evaluated in Study 109MS306 (CONNECT), an open-label, randomised, active-controlled study. Part 1 is included in the Tecfidera Paediatric Investigation Plan. The study has enrolled 156 subjects, and Part 1 was completed 12 November 2020.

It should be noted that there are no product-specific data for DRF in the paediatric population. So far, there are limited data for DMF in the paediatric population in a total of 34 subjects, aged 13 to18 years old (Studies 109MS202 and its extension Study 109MS311). These limited data collected after administration of DMF are not considered useful information to be included in the SmPC of DRF.

2.6.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable.

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

In addition to presenting the results from the individual pivotal Phase 3 Studies 109MS301 and 109MS302, the results from an integrated analysis of the two studies could allow for a more precise estimate of the treatment effect of DMF vs. placebo. Pooling of data from the two studies is considered achievable, according to the applicant, because of the similarity in study design, randomisation ratios, and patient populations as follows:

- Both studies were multicentre, placebo-controlled, parallel-group studies with an equal randomisation ratio to each treatment group.
- Both studies included the same dose regimens of DMF, and both included a DMF-matching placebo control group.
- In both studies, the same efficacy endpoints were assessed at the same time-points.
- Both studies provided consistent criteria and definitions of protocol-defined clinical relapses and disease progression. In both studies, the same INEC members were involved in confirming clinical relapses.
- Both studies included a similar patient population as reflected by key inclusion and exclusion criteria and more importantly, as demonstrated by the similar demographic and baseline disease characteristics of the recruited populations. The countries from which the participants were recruited were mostly the same, although the accrual patterns across regions were different between studies.

The pooled data provide an integrated assessment of the overall efficacy of DMF relative to placebo, as well as an assessment of efficacy in subgroups of participants. Demographics and baseline disease characteristics for each study were reviewed for consistency between studies before the integrated analysis. The individual study results (treatment effects) for the primary, secondary, and tertiary endpoints were also reviewed for consistency before the integrated analyses were performed. The applicant clarified that, if the treatment effects for a particular endpoint were not consistent between studies, the pooled analysis for that endpoint was not performed.

- **Studies 109MS301 and 109MS302 efficacy endpoints**

Both acute clinical relapses and accumulated neurological deficits, which result in increased disability over time, significantly impair the quality of life of MS subjects. The primary, secondary and tertiary endpoints (clinical and radiological measures) and their respective analyses were similar in both studies (109MS301 and 109MS302) and this allowed integrated analyses of the pooled results from these studies.

Table 18: Summary of Annualised Relapse Rate (INEC Confirmed) at 2 Years

	Study 301			Study 302			Pooled Analysis (301 + 302)		
	Placebo	BG00012 240 mg BID	BG00012 240 mg TID	Placebo	BG00012 240 mg BID	BG00012 240 mg TID	Placebo	BG00012 240 mg BID	BG00012 240 mg TID
No. (%) of subjects	408 (100)	410 (100)	416 (100)	363 (100)	359 (100)	345 (100)	771 (100)	769 (100)	761 (100)
No. (%) of subjects with									
0 relapses	237 (58)	312 (76)	321 (77)	223 (61)	266 (74)	269 (78)	460 (60)	578 (75)	590 (78)
1 relapse	115 (28)	75 (18)	64 (15)	83 (23)	71 (20)	51 (15)	198 (26)	146 (19)	115 (15)
2 relapses	44 (11)	19 (5)	20 (5)	44 (12)	14 (4)	21 (6)	88 (11)	33 (4)	41 (5)
3 relapses	8 (2)	1 (<1)	9 (2)	11 (3)	7 (2)	3 (<1)	19 (2)	8 (1)	12 (2)
4 or more relapses	4 (<1)	3 (<1)	2 (<1)	2 (<1)	1 (<1)	1 (<1)	6 (<1)	4 (<1)	3 (<1)
Total no. of relapses	246	128	140	212	124	106	458	252	246
Total subject-years followed	612.35	628.61	633.48	561.43	552.99	529.80	1173.8	1181.6	1163.3
Unadjusted rate[1]	0.402	0.204	0.221	0.378	0.224	0.200	0.390	0.213	0.211
Subject rate: mean[2]	0.550	0.242	0.244	0.497	0.266	0.315	0.525	0.253	0.277
Adjusted rate[3]	0.364	0.172	0.189	0.401	0.224	0.198	0.371	0.191	0.191
95% CI	0.303,0.436	0.138, 0.214	0.153, 0.234	0.329,0.488	0.179, 0.282	0.156, 0.252	0.326, 0.423	0.164, 0.224	0.163, 0.224
Rate ratio[3, 4, 5]		0.473	0.521		0.560	0.495		0.515	0.515
95% CI		0.365, 0.613	0.404, 0.670		0.423, 0.740	0.369, 0.662		0.427, 0.621	0.427, 0.622
p-value[3,5]		< 0.0001	< 0.0001		< 0.0001	< 0.0001		< 0.0001	< 0.0001

[1] for the treatment group, total number of relapses/total subject-years followed; [2] for each subject, (number of relapses/years followed)x365, then averaged over the treatment group; [3] estimated from negative binomial regression; [4] ratio of active to placebo; [5] versus placebo.

2.6.5.6. Supportive studies

The Phase 1 studies can be considered supportive for the dose selection for the Phase 3 studies with DRF. The four studies performed with Tecfidera (DMF) C-1900, 109MS301, 109MS302 and 109MS303 provide relevant efficacy data for the active moiety MMF subsequently to the administration of DMF.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The applicant has already clarified that no formal efficacy studies using typical MS disease endpoints with DRF have been completed or are ongoing. Their development strategy was based upon the bioequivalent exposure levels of MMF after oral dosing of DRF 462 mg and DMF 240 mg and a PK bridging approach between DRF and DMF.

The clinical programme for DRF includes ten completed Phase 1 studies and one completed and one ongoing Phase 3 studies.

The assessment of efficacy for DRF relied on the DMF clinical study programme which consists of one Phase 2 placebo-controlled study (Study C-1900), two Phase 3 studies, one placebo controlled (Study 109MS301) and one placebo and active controlled (Study 109MS302) and the final results from the extension Study (109MS303) of the two Phase 3 studies. All studies included RRMS patients.

<u>ALK8700-8700 (DRF) clinical efficacy data</u>

Study A302 (EVOLVE-MS-2)

A Phase 3, DB randomised multicentre study evaluated the comparative GI tolerability of DRF and DMF in adult subjects with RRMS (Study A302 [EVOLVE-MS2]). This study was conducted with adaptive design in two parts (Parts A and B). Parts A and B were identical in study design and included a 5-week, double-blind treatment period with two blind treatment arms (DRF and DMF). 120 eligible subjects were

randomised to one of the two treatment groups in Part A (n = 60 per group). Following completion of Part A, the applicant conducted a planned, unblinded exploratory analysis of the Part A GI tolerability and safety data to inform the endpoint selection for the overall study. The number of subjects in Part B were 386 (194 in the ALKS 8700 group and 192 in the DMF group).

Subjects were randomised in a 1:1 ratio to DRF 462 mg BID, taken orally and DMF 240 mg BID, taken orally (both treatments had a 1-week titration).

GI tolerability was determined using IGISIS and GGISIS. A number of secondary, exploratory and other endpoints have been also used for assessment.

Study A301 (EVOLVE-MS-1)

A Phase 3, OL single arm safety study of DRF (Study A301 [EVOLVE-MS1], ongoing) using exploratory efficacy, clinical, and MRI endpoints attempts to evaluate the long-term safety and tolerability of ALKS-8700 in adults with RRMS.

In this multicentre study, ALKS-8700 was administered up to 96 weeks for the treatment of RRMS. The target population for this study was adults, aged 18 to 65 years, diagnosed with RRMS. The study was to be conducted at approximately 125 sites in North America and Europe.

Subjects entered into the study in one of two ways:

1. De Novo Subjects: those who had not participated in any prior study of ALKS-8700.
2. Rollover Subjects: those who had completed the Treatment Period of Study ALK-8700 A302.

For de novo subjects, the study duration was up to 102 weeks, which included up to 4 weeks for screening, a 96-week open-label treatment period, and a 2-week follow-up period.

A total of 1057 subjects were enrolled in this study; 593 were de novo participants who received ALKS-8700 and 464 were Rollover subjects from Study ALK-8700 A302 (239 subjects had previously been treated with ALKS-8700 (DRF), and 225 participants had previously been treated with dimethyl fumarate [DMF]).

Treatment ALKS-8700 dose at 462 mg BID was received from Day 1 or Day 8 depending on whether the subjects had previously received DRF or DMF

In addition to assessment of safety, typical MS disease related endpoints were also used such as MRI endpoints (GdE lesions, new or enlarging T2 hyperintense and new unenhanced T1 hypointense lesions and PBVC. Clinical Efficacy Endpoints such as proportion of participants with MS relapse, ARR, progression of disability on the EDSS scores, proportion of participants experiencing progression of disability, NEDA, and T25FW were also used.

<u>Tecfidera (DMF) clinical efficacy data</u>

C-1900

The dose-ranging study C-1900 was 48 weeks and included 2 parts lasting 24 weeks each. Part 1 was DB placebo-controlled, in Part 2 (uncontrolled, dose-blinded extension portion of the study) subjects who received DMF (BG00012) in Part 1 continued on their randomised DMF (BG00012) dosing regimen, and subjects who received placebo in Part 1 were switched to DMF (BG00012) 240 mg TID. In this dose-ranging study patients received DMF (BG00012) 120 mg per day, 360 mg per day or 720 mg per day for 24 weeks. The primary endpoint in this proof of concept study was the total number of new Gd-enhancing lesions from MRI scans performed at Weeks 12, 16, 20, and 24 (calculated as the sum of the 4 MRI scans).

Study 109MS301 (DEFINE)

Study 109MS301 was a Phase 3, randomised, multicentre, DB, rater-blind, placebo-controlled, dose comparison study designed to determine the efficacy and safety of two doses of DMF (BG00012) in subjects with RRMS. The sample size for this study was planned to be approximately 1010 subjects. Subjects were randomised in a 1:1:1 ratio to DMF 240 mg BID, DMF 240 mg TID, or matching placebo. In study 109MS301 and Study 109MS302 two different doses of DMF (BG00012) have been used: 240 mg TID and 240 mg BID.

An Independent Neurology Evaluation Committee was established to re-assess relapses that were already defined by the examining neurologist. The primary endpoint, proportion of patients relapsed at two years was considered adequate in recent national scientific advices. ARR was included as secondary endpoint. A number of sensitivity analyses was performed. Time to disability progression was chosen as a secondary endpoint.

The study included a two-year treatment period (96 weeks), plus a Follow-up Visit at Week 100 for subjects who completed treatment and did not enter the extension study. Subjects were to receive study treatment (DMF (BG00012), placebo, or GA) for 96 weeks. GA, which has been approved for the treatment of MS in Europe since 2000, was chosen as active comparator is considered adequate as comparator in this study.

Study 109MS302 (CONFIRM)

Study 109MS302 was a Phase 3, randomised, multicentre, DB, rater-blind, placebo-controlled, dose comparison, active reference comparator study designed to determine the efficacy and safety of two doses of DMF in participants with RRMS. The sample size for this study was planned to be approximately 1230 subjects. Subjects were randomised in a 1:1:1:1 ratio to DMF 240 mg BID, DMF 240 mg TID, DMF-matching placebo, or GA 20 mg subcutaneous injection four times a day. The duration of study treatment administration was to be 96 weeks, with clinic visits every 4 weeks.

The primary endpoint was ARR and the proportion of participants relapsed was a secondary endpoint in this study. Other endpoints for both Studies 109MS301 and 109MS302 included: number of new or newly enlarging T2 hyperintense lesions, number of GdE lesions, number of new T1 hypointense lesions, disability progression measured by EDSS, MSFC, EQ-5D and VAS, SF-36, brain atrophy and whole-brain magnetisation transfer ratio.

These two Phase 3 studies had a duration of two years.

Study 109MS303 (ENDORSE)

This was an extension to the two Phase 3 studies, Study 109MS301 and Study 109MS302. Eligible subjects from Studies 109MS301 and 109MS302 were enrolled at week 96 (visit 24) of their previous BG00012 study, which served as the baseline visit for the extension study and followed for at least 8 years. Approximately 1700 patients with RRMS were planned to be enrolled at approximately 375 sites worldwide.

The first phase was a multicentre, parallel-group, randomised, dose-blind, dose-comparison period in which subjects received either of the following:

- BG00012 240 mg BID (2 capsules [120 mg each] BID and 2 placebo capsules once a day) or
- BG00012 240 mg TID (2 capsules [120 mg each] TID)

Subjects randomised to BG00012 in Studies 109MS301 or 109MS302 continued on the same BG00012 dose. Subjects randomised to placebo in Study 109MS301 or 109MS302 or to GA in Study 109MS302 were randomised to BG00012 240 mg BID or 240 mg TID in a 1:1 ratio. Subjects who switched to an alternative approved MS therapy in Study 109MS301 or study 109MS302 were randomised as outlined above according to their original treatment group in the two parent studies.

After Tecfidera had been approved for the treatment of multiple sclerosis at a dose of 240 mg BID, the study became an OL, single-dose study in a second phase where all patients received the marketed dose of 240 mg BID (2 capsules [120 mg each] BID), e.g., all subjects receiving BG00012 240 mg TID switched to BID (approved dosage) at their next study visit, once protocol Version 3 (17 March 2014) has been implemented.

A total of 2079 subjects completed the parent studies, Studies 109MS301 and 109MS302. Of these 1738 Subjects (84%) were enrolled in the extension study, all of them were enrolled in the dose-blind first phase of the extension study. 1736 patients received at least 1 dose of study treatment.

In addition to the evaluation of long-term safety, Study 109MS303 investigated the long-term efficacy of BG00012 using clinical endpoints (including proportion of patients relapsing and ARR) and disability progression (EDSS) and the long-term effects of DMF (BG00012) on MS brain lesions on MRI scans in patients who had MRI scans.

Efficacy data and additional analyses

No formal efficacy studies using typical MS disease endpoints with DRF have been completed or are ongoing. Dedicated pivotal studies comparing head-to-head the efficacy of DRF and DMF in RRMS, using efficacy assessments of relevant to MS primary endpoints have not been performed either. DRF can rather be considered a prodrug leading to the main active moiety/metabolite, MMF, which has already been sufficiently investigated with DMF. Hence, the development strategy for DRF was based upon the bioequivalent exposure levels of MMF after oral dosing of DRF 462 mg and DMF 240 mg and a PK bridging approach between DRF and DMF.

The approach of the applicant to try to demonstrate better GI tolerability with DRF compared to the approved Tecfidera (DMF) can be followed. GI symptoms have been observed in previous studies with DMF (BG00012). A large percentage of subjects in DMF studies (up to 35%) had a GI disorder in Study 109MS303. The incidence of GI disorders was highest in the first year of Study 109MS303 (ranging from 17% to 39% of participants). The most frequent AEs by PT (occurring in more than 5% of participants) were diarrhoea (230 subjects, 13%), upper abdominal pain (145 subjects, 8%), nausea (117 subjects, 7%), and abdominal pain (106 subjects, 6%). A total of 63 subjects (4%) discontinued treatment due to a GI disorder, and 63 subjects (4%) withdrew from the study due to a GI disorder.

Study A302

Endpoints – Scales IGISIS and GGISIS

Investigation of the GI tolerability was performed using two scales (IGISIS and GGISIS) for scoring the intensity of the symptoms by the subjects. It should be admitted that patient reported intensity scores in GI symptomatology is not expected to be too complicated. Scoring relatively common symptoms such as nausea, vomiting, upper abdominal pain, lower abdominal pain, and diarrhoea using scales such as an 11-point numeric rating scale ranging from 0 (did not have) to 10 (extreme) should be straightforward. How much each symptom interfered with the ability to accomplish regular daily activities with a 5-point Likert scale ("Not at all" <"Slightly" < "Moderately" < "Quite a bit" < "Extremely")] is also not expected to create difficulties for use by the patients and subsequently in detecting and showing differences between treatments.

However, there are several issues with the choice of the scales for the investigation of GI tolerability, namely the IGISIS and GGISIS scales:

- These scales were PROs and patients responded to the questionnaires using e-diaries. Bias could be an inherent characteristic of such a PRO compared to more reliable clinician reported outcomes.

- Validation for these two scales has not been reported. As admitted by the applicant these two patient-assessed GI tolerability scales have not been previously used in a clinical trial setting and were tailored to capture the most relevant GI symptoms related to DMF treatment.
- The literature reports on these two scales are associated only with DMF or DRF and it appears that these scales have not been used/validated during the investigation of other medicinal products, either.
- The fact that these scales were not validated and used for the first time in a clinical setting in a questionable study design to perform a comparison between DMF and DRF cannot be supportive of a better GI tolerability of DRF.
- The publications the applicant is referring to, are using different versions of these scales:
    - Paolini et al. (2008) describes the utility of the FSQ, a quantitative tool to assess patient-reported flushing endpoints. The results show that the FSQ is a useful patient-reported outcome measure to objectively assess flushing associated with extended-release niacin.
    - Fox et al. (2016) used questionnaires, which were based on and adapted from validated flushing questionnaires used in studies of niacin (Norquist et al. 2007). The MOGISS assessed global GI events (defined as one or more of the following symptoms: nausea, diarrhoea, upper abdominal pain, lower abdominal pain, vomiting, indigestion, constipation, bloating, and flatulence) and their effect on the patient during the 24 hours before each morning dose. The MAGISS assessed individual acute GI-related symptoms (nausea, diarrhoea, upper abdominal pain, lower abdominal pain, vomiting, indigestion, constipation, bloating, and flatulence) that the patient experienced during the 10 hours after each morning and evening dose.
    - Norquist et al. (2007) developed and validated a patient-reported FSQ. The primary flushing endpoint of the study was based on the single GFSS, an item within the FSQ, which assesses overall flushing severity on a 0–10 discretised analogue scale.

IGISIS and GGISIS scales have been used similarly to the FSQ. During validation of the FSQ, the percentage of days with a score above a threshold of 1 and 4 were found to significantly discriminate among groups using FSQ. However, it is still unclear what difference between the assessed therapies constitutes a minimally significant or a clinically meaningful difference for IGISIS and GGISIS.

Study A302 findings

In study A302 for the pooled data in Parts A and B, the mean values of event days for observed diaries (i.e., all diaries collected, without imputation of any values) were 1.5 days and 2.5 days for the primary endpoint, Number of Days with Any IGISIS Symptoms Intensity Score ≥2, for the DRF and DMF groups, respectively. This was adjusted for study parts, region (US and non-US), age, and BMI and led to a rate relative to the exposure days of 0.041 for the DRF group, which was lower than the rate 0.076 for the DMF group. The rate ratio for the pooled Parts A and B was 0.542 (95% CI [0.390, 0.754]) with a corresponding p=0.0003, representing a potentially relative reduction in GI symptoms of 45.8% in the DRF group compared with the DMF group. The applicant is claiming that in Study A302 the primary endpoint was achieved and a statistically significant reduction (46%) in the number of days with an IGISIS symptom intensity score ≥ 2 was observed for participants treated with DRF compared with DMF-treated participants. Statistically significant differences have been also demonstrated in the FAS populations for the part B only (0.520, p = 0.0007). It is noted that Part B results (key secondary endpoint) were significant and consistent with the pooled results. Only Part B data can be considered as confirmatory, whereas the pooled analysis (Part A and B combined) is considered as supportive only. Since both analyses yield comparable results, the issue is not further pursued. It should be pointed out

however, that the GI tolerability primary endpoint for study A302 was the Number of days with any IGISIS individual symptom intensity score ≥ 2 relative to exposure days in Part A and Part B combined.

Furthermore, Part A was exploratory, and the findings were not statistically significant. As already mentioned, combining the results of Part A and Part B cannot be considered appropriate to substantiate a claim for better GI tolerability. The results which were not statistically significant, all numerically favoured diroximel DRF.

Table 19: Summary of rate ratios of DRF vs DMF with different IGISIS cut-off points in the scores

	Rate Ratio* of DRF VS DMF in Part A	Rate Ratio* of DRF VS DMF in Part B	Rate Ratio* of DRF VS DMF in Part A+B
IGISIS ≥ 1	(0.820)[#]	(0.735[#]	0.714
IGISIS ≥ 2	0.654	0.520	**0.542**
IGISIS ≥ 3	(0.684)[#]	(0.583)[#]	0.555

This table was constructed by the assessment teams
*rate ratio of mean Total number of days relative to exposure with any IGISIS intensity score ≥ 1, 2 or 3 in the overall study population
[#]rough calculations from the graphs (Figures 1 and 2) provided by the applicant in the Day120 responses

In order to put percentages in a numerical perspective and in terms of discontinuations, 4 subjects on ALKS 8700 (DRF) discontinued the study due to adverse events and 15 subjects in the DMF group. From these discontinuations, 0.8% in ALKS-8700 (DRF) were due to gastrointestinal disorders, whilst in the case of DMF group these were 4.8%. Out of these, one subject on ALKS-8700 (DRF) discontinued due to diarrhoea and one due to vomiting. In the case of DMF five subjects discontinued due to upper abdominal pain, three due to diarrhoea, three due to abdominal pain, two due to vomiting, one due to abdominal distention, one due to gastrointestinal pain and one due to nausea. An analysis for discontinuations in Part B alone could have provided additional information, but the numbers are very low to allow any meaningful conclusions.

As already pointed out above in the endpoints section, the approach of the applicant to examine the unblinded data from exploratory part A, then proceed to Part B and finally analyse the pooled results from both parts is not considered valid. Hence, only Part B results are to be considered for the main conclusion. However, also part B data show a significant difference.

The differences observed after short term treatment, could have been indicative of better GI tolerability in favour of DRF compared to DMF. However, issues with the findings of study A302 still remain and prevent a claim for better GI tolerability for DRF:

a) The informative value of the results based on scales which have not been used before (please see also endpoints).

The numbers are too low to draw any meaningful conclusions. The findings show some differences between ALKS-8700 (DRF) and DMF. However, the selected GI TEAEs include MedDRA preferred term: nausea, vomiting, abdominal pain, abdominal pain upper, abdominal pain lower, and diarrhoea) could have been summarised in nausea, vomiting, diarrhoea and abdominal pain. In that case, it is

questionable how many differences would have been detected, especially with the scoring system used (i.e., event days). The lack of reproducible results in a different study and the development of the IGISIS and GGISIS scales specifically for the Study A302 creates concerns.

Furthermore, irrespective of the analysis used for the rate, the Number of Days with any IGISIS Symptom Intensity Score ≥ 2 relative to exposure days and consequently the rate remain very low in both treatment groups (**Table 20**).

Table 20: Summary of the number of days with any IGISIS symptom intensity score ≥ 2 and the rates

	Part A+B FAS ALKS 8700 (N=253)	Part A+B FAS DMF (N=253)
Number of Days with any IGISIS Symptom Intensity Score ≥2	1.5	2.5
Rate with Poisson Regression Model for Number of Days with any IGISIS Symptom Intensity Score ≥2	0.042	0.071
Rate with Zero-inflated Negative Binomial model for Number of Days with any IGISIS Symptom Intensity Score ≥2	0.225	0.338
Rate with Negative Binomial Model for Number of Days with any IGISIS Symptom Intensity Score ≥2	0.045	0.080
	Part B FAS ALKS 8700 (N=194)	Part B FAS DMF (N=191)
Number of Days with any IGISIS Symptom Intensity Score ≥2	1.3	2.2
Rate with Poisson Regression Model for Number of Days with any IGISIS Symptom Intensity Score ≥2	0.034	0.060
Rate with Zero-inflated Negative Binomial model for Number of Days with any IGISIS Symptom Intensity Score ≥2	0.148	0.242
Rate with Negative Binomial Model for Number of Days with any IGISIS Symptom Intensity Score ≥2	0.037	0.068

This table was constructed by the assessment teams

b) The robustness of the statistical analyses with respect to the ambiguous pre-specification and the considerable amount of non-evaluable diaries (please refer to the statistical methods).

The robustness of the analysis regarding the large amount of non-evaluable diaries still remains unclear, especially since a reference based multiple imputation approach was apparently not performed in an appropriate way. (please see below)

c) The study duration of the "confirmatory" Part B of the study, which was very short (five weeks), taking into account that the DRF and DMF are intended for long-term use.

It is acknowledged that GI tolerability events are a known, transient side effect for DMF, typically occurring early in therapy, within the first 1 month. However, it is also noted that a five-week duration may not be optimal to be able to fully describe the overall adverse event profile of DRF compared to DMF, nor will it characterise fully the time to onset, duration, resolution of all adverse events and provide a full picture of subjects' conditions. The absence of a placebo group in Study A302 increases the uncertainty concerning the findings. Taking into consideration the transient character of the GI tolerability AEs, which after 1 month move into an incidence similar to that of placebo together with the

very low numbers, it is difficult to make any clinically significant statements for potential differences between DRF and DMF treatment.

As reported by the applicant, the number of days with any IGISIS individual symptom intensity score ≥ 2 (event days) is counted in the diaries. As the IGISIS is performed twice a day, the applicant provided some clarifications whether a day with only one IGISIS questionnaire meeting the criterion and a day with two IGISIS questionnaires meeting the criterion equally count as one event day. It is unlikely that these two situations may represent the same severity and impact on daily activities (e.g., for a subject currently employed, symptoms during the first dose may have higher impact than symptoms during the second dose, considering standard working hours). Furthermore, in the IGISIS scale, if a symptom was assessed as ongoing, it was only recorded in the initial intensity score. Therefore, the applicant was asked to comment on which of the analysed parameters of the IGISIS scale allowed for the assessment of the severity of the side effects, which increased in intensity over time (A302).

The applicant provided an example whereby a subjects records an ongoing symptom of nausea in the morning diary with an intensity score of 3 and over the course of the day, and when this nausea is worsened, the participant is requested to end the previous nausea symptom and enter a new nausea symptom with a newly categorised intensity score (for example, 6). This approach may not be a true reflection of the clinical condition of the patient. It does not truly represent the worsening or the deterioration of the symptom and may provide a false picture of the symptom, introducing a bias. The same applies to recording a lower intensity score for a symptom that improves. The assumption that the symptom is unchanged until the symptom ended, or symptom severity changed appears unverifiable, it would correspond to a last observation carried forward approach and creates a potentially biased outcome.

The applicant also clarified that one event day was counted when a patient recorded more than one symptom in a day with a symptom score ≥ 2 and that one event day was also counted in case a symptom ended in the afternoon and another symptom started.

According to the applicant, the worst (i.e., highest) recorded score for each symptom was used when assessing the score for that day. Therefore, a day with at least one IGISIS questionnaire meeting the criterion of a symptom intensity score ≥ 2 counted as 1 event day. For example, if a participant recorded a score of 3 in the morning and 1 in the evening, this participant would have contributed one day with a score ≥2 to the analysis. A day with two IGISIS questionnaires meeting the criterion also counted as 1 event day. For example, if a subject recorded a score of 2 in the morning and 3 in the evening, this subject would have contributed one day with a score ≥ 2 to the analysis. It appears that a day with at least one IGISIS questionnaire meeting the criterion and a day with two IGISIS questionnaires meeting the criterion both counted as 1 event day. These cases were both counted as 1 event day, the same as in the case of one symptom having a score ≥ 2 in a day (please see Table 24). From this it can be assumed that a patient recording multiple symptoms would have also counted as 1 event day despite that the patient recorded more than 1 symptoms per day.

The applicant has performed, upon request, an analysis comparing the number of event days with two or three different GI symptom scores ≥ 2 between treatment arms for Part A and Part B FAS population and for only Part B FAS population. As already pointed out previously, the analysis from both part A and part B cannot be considered acceptable.

The applicant has calculated the rate ratio using the exposure days and concluded that "*these analyses are similar to the primary endpoint from Study A302, showing an approximate 60% to 73% reduction on the number of days with an Individual Gastrointestinal Symptom Impact Scale (IGISIS) score of ≥ 2 relative to exposure for diroximel fumarate (DRF) when compared with dimethyl fumarate (DMF)*". However, this conclusion cannot be agreed upon. From a different approach, for Part B FAS population

the Summary of number of days with at least two IGISIS symptoms intensity scores ≥ 2 was 0.5 for DRF and 1.0 for DMF, respectively. Therefore, the difference between the two treatment groups is half a day with at least two IGISIS symptoms intensity score ≥ 2 in a total of approximately 35 exposure days (~1.4%). For the same population the Summary of number of days with at least three IGISIS symptoms intensity scores ≥ 2 was 0.2 for DRF and 0.4 for DMF, respectively. Therefore, the difference between the two treatment groups is 0.2 of a day in a total of approximately 35 exposure days (~0.6%).

The event days with at least 1 IGISIS symptoms intensity scores ≥ 2 were 1.67 for DRF and 2.51 for DMF (providing that the imputation analysis was the appropriate one) with a difference between treatments of one day in a total of approximately 35 exposure days (~2.4%) (**Table 21**).

Table 21: Summary of the number of days with any, or with 2 or 3 IGISIS symptoms intensity Score ≥ 2, rate ratios and differences between treatment groups – Part B (FAS Population)

Analysis	**Rate Ratio (95%CI) p-value**	**Mean (SD) Number of Days With at Least 2 IGISIS Symptoms Intensity Score ≥ 2**		**Difference in days between treatment groups** (~% of exposure days)
		DRF	**DMF**	
Mean Number of Days of Exposure (SD)		35.2 (3.80)	33.7 (6.31)	
Summary of number of days with any IGISIS Symptom Intensity Score ≥ 2 - Part B FAS population[1]	0.590 (0.439, 0.795) p = 0.0011	1.67 (0.77)	2.51 (1.19)	**0.84** (2.4)
Summary of number of days with at least 2 IGISIS symptoms intensity scores ≥ 2 - Part B FAS population[2]	0.386 (0.219, 0.680) p = 0.0010	0.5 (1.69)	1.0 (2.39)	**0.5** (1.4)
Summary of number of days with at least 3 IGISIS symptoms intensity scores ≥ 2 - Part B FAS population[2]	0.269 (0.121, 0.602) p = 0.0014	0.2 (0.73)	0.4 (1.19)	**0.2** (0.6)

This Table was constructed by the assessment teams
[1]From Table 2 in Question 22 (providing that the imputation analysis is the appropriate one)
[2]From Table 1 in Question 20

Clinical relevance of A302 findings

The clinical relevance of the results in this study (A302) was also discussed:

a) It is still unclear what difference in the scales used in the Study A302 constitutes a minimal significant clinical difference (the primary endpoint was pre-defined as the number of days IGISIS individual symptom intensity score ≥ 2).

b) Days with intensity ranging from 2 to 10 were counted as events. The applicant was invited to further justify the selection of this cut-off and to discuss if values closer to the lower limit of the range (e.g., 2, 3, 4) truly represent clinically meaningful adverse events.

The applicant has chosen the number of days any IGISIS Symptom Intensity Score ≥ 2 relative to exposure days (which are approximately 35) as the primary endpoint and not intensity scores ≥ 1, ≥ 3, ≥ 4, ≥ 5 or ≥ 6. The cut-off value of 2 for IGISIS symptom severity score was shown to have high sensitivity (90%) and moderate specificity (~59%) to detect moderate and severe select GI tolerability TEAEs (TEAEs of diarrhoea, nausea, abdominal pain upper, abdominal pain lower, and vomiting).

According to the applicant, in Study A302, the primary endpoint (for part A and part B FAS population) was achieved and a statistically significant reduction (46%) in the number of days with an IGISIS symptom intensity score ≥ 2 was observed for participants treated with ALKS-8700 (DRF) compared with DMF-treated participants (rate ratio [95% confidence interval]; 0.54 [0.39-0.74]; p = 0.0003). After a requested multiple imputation analysis, in Part A and Part B, the mean (95% confidence interval [CI]) number of event days for imputed diaries were 1.96 days (1.519, 2.395) and 2.86 days (2.282, 3.447) for the DRF (ALKS 8700) and DMF groups, respectively. The rate (95% CI) obtained from the negative binomial model was 0.050 (-0.151, 0.251) for the DRF group, which was lower than the 0.081 (-0.109, 0.271) in the DMF group. The rate ratio (95% CI) was 0.618 (0.352, 0.885), with a corresponding p = 0.0050.

In the case of number of days any IGISIS Symptom Intensity Score ≥ 1 for Part A and B combined, the results for ALKS-8700 (DRF) and DMF were 2.9 and 3.9, respectively. But the rate ratio, albeit statistically significant, was 0.714 indicating only small differences in favour of ALKS 8700 (DRF) and a potential reduction of 28.4% in the number of days with an IGISIS symptom intensity score ≥ 1 compared to the claimed reduction of 46% in the number of days with an IGISIS symptom intensity score ≥ 2.

c) It is noted that the Number of Days with any IGISIS Symptom Intensity Score ≥ 3 is below 1 for ALKS 8700 (DRF) (0.9) for Part A and B combined and Part B only (0.7). These numbers are very low to draw any clinically meaningful conclusions and are questioning the clinical usefulness of these scales. Even lower numbers were found for the Number of Days with any IGISIS Symptom Intensity Score ≥ 4, 5 and 6, whilst these scores would have been expected to have more clinical significance. The numbers with any IGISIS Symptom Intensity Scores ≥ 3, 4, 5 and 6 are very low to draw any clinically meaningful conclusions and are questioning the clinical usefulness of these scales. The clinical relevance of the choice of the endpoint is still not established. One could argue that a result—driven approach was applied for the choice of intensity score ≥ 2. The applicant also, upon request, discussed why the Number of Days with any IGISIS Symptom Intensity Score ≥ 2 relative to exposure days is an appropriate endpoint to provide a clinically relevant and meaningful outcome. However, it could not be robustly demonstrated that the Number of Days with any IGISIS Symptom Intensity Score ≥ 2 relative to exposure days is an appropriate endpoint to provide a clinically relevant and meaningful outcome. The number of event days are very small. Even with an IGISIS symptom intensity score ≥ 2 the difference between the DRF and the DMF group was approximately one day. Differences in the percentages of subjects with GI TEAEs and in the percentages of mean duration in days between the two groups were also very small. Additional calculations were needed in almost all analyses presented up to now, in order to show a reduction in GI AEs and an advantage in favour of DRF.

It should be pointed out that these results were the outcome of non-validated scales, used for the first time in a clinical setting with a questionable study design. The clinical meaningfulness of these results is still unclear.

GGISIS, which assessed symptoms daily (as opposed to IGISIS assessed twice a day) accounting for the totality of GI symptoms and most importantly, for the overall interference of these symptoms on daily activities may have been preferred. The applicant was invited to justify the selection of IGISIS instead of GGISIS as primary endpoint and the item relative to intensity instead of the one relative to interference in daily activities.

It is acknowledged that there was no previous experience with the use of IGISIS and GGISIS scales to inform statistical assumptions, it was unknown which scale would be considered sensitive enough to detect a difference between groups.

It is also acknowledged that the GGISIS scale, while informative, was also less sensitive than the IGISIS, since: the GGISIS scale was administered once daily (compared to twice for the IGISIS) and GGISIS scale asked subjects to recall and assess the intensity of GI symptoms in general. The evaluation of the number of days with a GGIGIS score ≥2 over the treatment period demonstrated worse findings for the primary endpoint (rate ratio [95% CI]: 0.67 (0.43–1.05), p = 0.082, compared to IGISIS. Between the two scales the choice for IGISIS can be justifiable.

Finally, it is considered that the "efficacy" findings for better GI tolerability are not in accordance with the safety GI ADRs. The applicant provided a discussion regarding the similarities in GI tolerability ADRs from a safety perspective and the findings from the IGISIS and GGISIS scales.

According to the applicant, there were numerical improvements in the incidence of all GI TEAEs in the DRF group compared to the DMF group (34.8% for DRF vs. 49% for DMF).

Table 22: GI TEAEs experienced in ≥5% of subjects in any treatment group during the treatment period (Safety population, parts A and B)

	Treatment Groups		
	ALKS 8700 (DRF) (N=253) n (%)	**DMF (N=251) n (%)**	**All Subjects (N=504) n (%)**
GI Disorders	88 (34.8)	123 (49.0)	211 (41.9)
Diarrhoea	39 (15.4)	56 (22.3)	95 (18.8)
Nausea	37 (14.6)	52 (20.7)	89 (17.7)
Abdominal pain upper	17 (6.7)	39 (15.5)	56 (11.1)
Abdominal pain	16 (6.3)	24 (9.6)	40 (7.9)
Abdominal pain lower	15 (5.9)	17 (6.8)	32 (6.3)
Vomiting	9 (3.6)	22 (8.8)	31 (6.2)

AE = adverse event; DMF = dimethyl fumarate; DRF = diroximel fumarate; N = total number of subjects; n = number of participants with AEs in a group; SOC = system organ class TEAE = treatment-emergent adverse event.
Note: If a subject experienced more than 1 AE in a category, the participant was counted only once in that category. Only categories (defined by preferred term) with ≥ 5% AEs in any group are displayed along with their corresponding SOC categories.

However, between the DMF and the DRF group, the differences in the percentages for specific GI AEs (%DMF-%DRF) such as Diarrhoea (6.9%), Nausea (6.1%), Abdominal pain upper (8.8%), Abdominal pain (3.2%), Abdominal pain lower (0.8%), and Vomiting (5.2%), which were the 5 domains of IGISIS questionnaire, were very small and their clinical significance to justify an advantage of DRF vs DMF is questionable. Taking also into consideration that these results derived from a study with two parts (Safety Population, Parts A and B), from which only the results from part B can be considered as appropriately analysed, then no robust conclusions can be drawn.

Mechanism and potential plausibility for better GI tolerability of DRF

The mechanism for better DRF tolerance is unclear. Both DMF and DRF undergo pre-systemic hydrolysis with an identical active metabolite (MMF). According to the applicant's declarations, the primary metabolite of DRF, HES is inactive. Therefore, the applicant was requested to justify what mechanism could lay behind the better tolerance of DRF.

The applicant presented a discussion of the probable basis for the better tolerability of DRF relative to DMF. Among the likely reasons for better gastrointestinal-related tolerance were the lower concentration of methanol formed, the larger particle size of DRF limiting binding to receptors within the gastrointestinal tract, and the lower electrophilicity of DRF.

Nevertheless, all these reasons are speculative. There is no evidence to support that any of the presented mechanisms are important in the hypothesised better tolerance of DRF.

Statistical analyses

In addition, Part B in Study A302, because of the adaptive design, the primary endpoint and sample size were finalised after the unblinded data from exploratory Part A have been examined. Due to this unblinded interim analysis after which the final version of the SAP was generated pooling of both parts cannot be accepted as a valid procedure. The primary analysis based on pooled Part A and Part B data is not acceptable due to the unblinded interim analysis with a potential type-1 error inflation and the finalisation of the SAP after the interim analysis. The analysis of the pooled data could therefore be biased. Only Part B data should be taken into account for the efficacy conclusions, if any, with respect to all analyses.

According to the applicant, there were consistent patterns of improvement favouring DRF in both Part A and Part B, which consisted of two separate study populations and these findings suggest that results can be reproduced utilizing these scales. This cannot be agreed. Reproducibility would have been achieved in case two different studies would have been conducted and produced the same outcome. The main analysis (if based on Part B data), i.e., the use of a negative binomial model for the number of days with any symptom intensity score ≥ 2 using the log number of exposure days as an offset parameter is acceptable in general. However, the analysis was not clearly specified with respect to potential additional covariates. In addition, it is not clear whether the envisaged conditional procedure where the use of the model depends on the outcome still maintains the type-1 error, although inflation may not be considerable. This may, however, not be considered as a relevant issue since the negative binomial model was finally used with the initially planned covariates. In order to show robustness, the applicant was requested to provide sensitivity analyses based on the proposed Poisson model with adjustment for overdispersion and the zero-inflated negative binomial model.

Furthermore, as the covariates were not properly pre-specified in the SAP (and age was added as an additional covariate), the analysis cannot be considered as fully pre-specified. The applicant was also requested to provide an analysis without the factor age as a covariate as well as additional sensitivity analyses with added relevant baseline covariates.

All requested sensitivity analyses have been provided with comparable results with the primary analysis.

The main issue in the analysis is based on the improper handling of missing evaluable diaries. For a considerable number of days, the diaries were not evaluable or valid, which may also include completely missing diaries. No missing data imputation was neither planned nor performed for these days. The analysis was based on the assumption that the absence of a valid diary (or evaluability of a diary) was completely at random and the actual endpoint refers to a mixture of the presence of relevant symptoms (≥ 2) and the evaluability of the diary. Hence, the applicant should justify the validity and robustness of the conclusions with respect to the large number of non-evaluable diaries and whether the actual analysis

yields an unbiased estimation for the relative reduction in days with any symptom intensity score ≥ 2, if all diaries were evaluable.

Furthermore, the applicant was requested to provide relevant sensitivity analyses using proper missing data imputation methods that show the robustness of the results including an analysis where the data on the non-evaluable days are imputed using reference based multiple imputation conditioned on baseline covariates and the day of treatment.

The applicant did not initially implement a reference based multiple imputation approach to show robustness of the results. A reference based multiple imputation approach should use the data from the reference group only to generate the distributions to be used for multiple imputation. This approach is required to assess robustness of the results by assuming no difference to the reference in case of missing data. The applicant provided an additional analysis. However, according to the description of the applicant it remained unclear whether this additional analysis corresponded to a reference-based multiple imputation. The applicant wrote that "five repetitions were obtained for analyses *to show robustness* of the missing imputation of the difference of treatment effect on the number of days with IGISIS symptom intensity score ≥ 2". It should be noted that multiple imputation would require the combination of multiply imputed datasets applying Rubin's rule.

The applicant finally provided a detailed description of the used approach, the SAS code used and the corresponding output, together with a proper reference-based multiple imputation with 20 repetitions applying Rubin's rule to combine the multiply imputed data sets. It is noted that the point estimate of the rate ratio increased slightly, but the confidence interval got much larger and the p-value increased likely due to the increased variability of the multiple imputation approach although the result remained statistically significant. It seems that the approach had not been correctly applied in the first version. Single imputation of the days starting with Day 39 might be debatable (underestimating the variance for these days), but it is understood that otherwise the estimation approach could have been unstable due to the low number of subjects with more than 38 days.

With respect to the other endpoints, MS disease relevant assessments using EDSS, T25-FW, SF-12, and EQ-5D-5L were not expected to be clinically meaningful given the short duration of the study, as admitted also by the applicant. However, some indications on the efficacy of DRF in MS could be obtained. These assessments could be considered supportive, complement the bioavailability/bioequivalence studies and provide further support for the approval of DRF based on DMF efficacy data.

Study A301

This ongoing, multicentre, open-label study was designed to evaluate the long-term safety and tolerability of DRF/ALKS 8700 administered up to 96 weeks for the treatment of RRMS as well as exploratory efficacy endpoints. The interim clinical data as of 07 February 2020 have been summarised. It can be agreed with the applicant that the demographic and baseline characteristics of the study population reflected those of the patient population with RRMS for whom DRF/ALKS 8700 would be indicated.

Mean exposure to study treatment for *the de novo,* DRF/ALKS 8700 Rollover, and DMF Rollover groups was 590.0, 426.5, and 446.3 days, respectively.

All efficacy analyses were exploratory in nature. After exposure to DRF/ALKS 8700 for up to 96 weeks, the key efficacy outcomes, including MRI endpoints and relapse rates, ARR and disability assessment (EDSS and T25-FW), were comparable to the findings from DMF Phase 3 studies and only minimally deteriorated from baseline. A low ARR 0.14 and a reduction in the mean number of GdE lesions (-0.082) was observed at week 96. The number of participants with confirmed disability progression sustained for 12 weeks was low across all groups (8.1% in the *de novo group*, 7.2% in the DRF Rollover group, and 8.9% in the DMF Rollover group). The mean change from baseline in T25-FW scores was 0.034, -0.178

and 0.822 seconds in the *de novo* group, the ALKS 8700 Rollover group, and the DMF Rollover group, respectively). Mean EDSS scores across enrolment groups were generally stable from Baseline up to Week 96. MRI endpoints showed a decrease in disease activity and stabilisation of disease following treatment with DRF/ALKS 8700 in those subjects continuing treatment. The results for other clinical outcome measures (disability progression, EDSS, NEDA-3, and T25-FW) showed a sustained effect on disease activity and were consistent with the MRI and ARR results. The results are favouring DRF in comparison with reported values for MS untreated subjects. These findings are clear indicators of the sustainability of a treatment benefit for DRF/ALKS 8700 (and its main active moiety MMF). Patient-reported outcomes did not show notable improvement from baseline. The SF-12 and EQ-5D-5L scores demonstrated overall stability or minor decreases over time.

The mean change from baseline in the GdE lesions count for the *de novo* group, the ALKS-8700 Rollover group, and the DMF Rollover group was -0.85, -0.49, and -0.97 lesions, respectively, which corresponds to 64.4%, 80.3%, and 80.2% decrease from baseline, respectively. Overall, there was an increase in the proportion of participants with 0 GdE lesions (20.7%) from Baseline to Week 96 as well as decreases in the proportions of participants with 1 to 4, 5 to 8, and ≥ 9 GdE lesions (-14.7%, -3.8%, and -1.9%, respectively) from baseline to Week 96. Across the 3 groups, a high proportion of participants (> 90%) had 0 GdE lesions at Week 96. The efficacy results for clinical and MRI endpoints in participants with RRMS treated with DRF in Study A301 showed treatment effects in line with expectations from data available for DMF.

DMF clinical efficacy data

These data have already been assessed during the MA procedure for Tecfidera (DMF, BG00012). According to the applicant, study C-1900 supported the continued development of the DMF 240 mg dose in the Phase 3 studies.

Results from the pivotal Phase 3 studies 109MS301 and 109MS302 demonstrated that DMF (BG00012) 240 mg BID consistently provided significant improvement compared with placebo in both clinical and MRI outcome measures and showed increased efficacy compared with an approved first-line therapy, GA, in subjects with RRMS. These results were confirmed by the integrated analyses of the two pivotal Phase 3 studies with DMF.

Altogether the evidence of clinical efficacy for DMF (BG00012) as a disease modifying therapy in patients with RRMS based on two Phase 3 studies is also supported by MRI outcome measures in the Phase 2 study.

Final results from extension Study 109MS303 showed that the majority of participants did not have disease progression as measured by an increase in EDSS (24-week confirmation). MRI assessments showed that the majority of participants within the MRI cohort had no GdE lesions and the number of GdE lesions remained low. Extension Study 109MS303 confirmed the maintained treatment effect of DMF (BG00012) 240 mg BID, with low relapse rates and confirmed slowing of the disability progression for up to ten years of treatment (Phase 3 studies combined).

Assessment of paediatric data on clinical efficacy

Any reference to the paediatric studies with DMF in the SmPC of Vumerity DRF currently cannot be justified since data are very limited.

2.6.7. Conclusions on the clinical efficacy

Since comparative bioavailability examination of DMF and DRF has shown bioequivalence (at the level of exposure to MMF), the efficacy results from the DMF clinical programme can be used to support efficacy claims for DRF. Both prodrugs DMF and DRF share the same active moiety, monomethyl fumarate (MMF), and the pivotal data (from Studies C-1900, 109MS301 and 109MS302) together with other supportive studies justified the approval of DMF in RRMS. However, the claim for additional benefit of improved GI tolerability of DRF compared to DMF has not been robustly demonstrated. Small differences between the two groups in the mean number of days with IGISIS symptoms intensity scores ≥ 2, using scales of questionable validity and specificity, with results from both parts A and B and from a single Study A302, cannot be considered as an appropriate justification to support an advantage in GI tolerability for DRF compared to DMF.

2.6.8. Clinical safety

The marketing application for DRF is founded on the principle of bioequivalent exposure of the active therapeutic moiety MMF after administration of 462 mg DRF and 240 mg DMF (the active substance of Tecfidera). Consequently, the efficacy and safety profiles of DRF and DMF are expected to be similar. Therefore, the clinical safety relies on the data already assessed for Tecfidera (EMEA/H/C/002601/0000/Rev 1).

The titration scheme in the DRF studies is analogous to that in the DMF studies. It implies initiation of either drug with half the maintenance dose at Day 1 (i.e., 231 mg DRF BID and 120 mg DMF BID), which is then to be increased to the full dose on Day 7 (i.e., 462 mg DRF BID and 240 mg DMF BID).

The clinical programme of DRF consists of ten completed Phase 1 studies (nine in healthy volunteers and one in subjects with renal impairment) and two Phase 3 studies in adult subjects with RRMS. Safety data have been presented separately due to differences in the study design for the two Phase 3 studies:

- the completed 11-week DB and active-controlled study A302 against DMF, with a five-week treatment period (including one week titration) and,
- the ongoing OL Study A301, which aimed to address safety and tolerability up to 96 weeks of DRF treatment in DRF and DMF rollovers from A302 and *de novo* subjects.

The safety population included all subjects who received at least one dose of study treatment in the Phase 1 studies and Phase 3 studies.

Safety presentation and discussion for the two Phase 3 DRF studies is based on the evaluation of TEAEs, Adverse event of special interest (AESIs), clinical laboratory testing, vital sign measurements, ECGs, and C-SSRS scores for the safety population.

Long-term safety data are so far limited and interim data derive from the ongoing OL Study A301 with the latest data cut-off of 01 September 2020. Final data of A301 is not expected within the course of this procedure.

Clinical safety of DMF focuses on the results of four clinical studies in adult RRMS subjects, i.e., one Phase 2 dose-ranging study (C-1900, 24 weeks of duration), two pivotal, placebo (and one also active) controlled Phase 3 studies (109MS301 and 109MS302; each of 96 weeks duration), and an eight year OLE Study 109MS303, for which interim data were available and assessed as part of the Tecfidera MAA (data cut-off 03 August 2011). Results of Study 109MS303 with data cut-off 08 November 2019 are under evaluation in a parallel procedure (EMEA/H/C/002601/II/0069/G) at the time of this assessment. DMF studies were pooled to assess short-term safety (Pool A; controlled DMF studies) and long-term clinical safety (Pool B; controlled and uncontrolled clinical studies).

2.6.8.1. Patient exposure

Overall extent of exposure

Across the DRF clinical programme, 1461 subject received at least one dose of DRF in 12 clinical studies. This includes 390 subjects in the Phase 1 studies with an exposure ranging from single doses up to 18 doses of study treatment over 10 days (366 healthy volunteers and 24 subjects with renal impairment).

1071 subjects received at least one dose of DRF in the Phase 3 studies A302 and A301 as per the original cut-off date 07 February 2020. The total extent of exposure to DRF in subjects forming the Phase 3 safety population with at least one dose of DRF amounts to a mean (SD) of 523.9 days (213.61). 972 subjects (88.6%) received DRF for more than six months. 826 subjects (75.3%) and 499 subjects (45.5%) received DRF for more than 12 months and 24 months, respectively, with a total subject-years of exposure to DRF of 1536.21 years.

In Study A301, the safety population comprised 1057 subjects, who received at least one dose of DRF, and who were allocated to three enrolment groups: 593 *de novo* subjects (who had not participated in any prior DRF study), 239 subjects in the DRF, and 225 subjects in the DMF rollover group from A302. Subjects in the *de novo* group were in the study for a longer time compared with subjects in the Rollover groups. The mean (SD) duration of exposure to DRF in Study A301 (data cut-off 01 September 2020) was 561.4 (190.43) days.

In Study A302, 504 of 506 enrolled subjects received at least one dose of DRF (253 in the DRF and 251 in the DMF group). The mean (SD) duration of exposure to study treatment in the overall population was 34.6 (5.34) days and the exposure was similar in the two treatment groups.

The integrated safety database for DMF (referred to as Pool B data) included 2468 subjects exposed to DMF (for a total duration of ~3600 subject years) and 836 subjects were exposed to placebo. 1477 of 2468 subjects (60%) were exposed to DMF for ≥48 weeks and 1056 subjects (43%) were exposed for ≥ 96 weeks.

Pool A (placebo-controlled) data served as the main dataset to allow for evaluation of treatment-related AEs with DMF 240 mg BID and the 240 mg TID doses up to two years of exposure and included 1720 subjects exposed to DMF (769 and 823 subjects, respectively, received DMF 240 mg BID and DMF 240 mg TID). 836 subjects received placebo. Pool A safety data provided a mean duration of exposure to 240 mg DMF (which results in an equivalent exposure to MMF as with DRF 462 mg BID) of 76.58 weeks. Pool B also includes patients with exposure to DMF up to four years.

At present, the longest exposure to DMF derives from Study 109MS303 with the final cut-off date 8 November 2019: 52% and 40% of patients were treated with DMF for ≥ 6 years and ≥ 8 years, respectively, and the median duration of exposure to study treatment (min, max) was 5.848 (0.00, 9.43) years.

Subject disposition and baseline characteristics in DRF phase 3 studies and DMF pools

As of the data cut-off date 01 September 2020 in Study A301, 659 of 1057 patients (62.3%) completed the study, 152 subjects are ongoing (14.4%), and 246 (23.3%) subjects discontinued the study. The main reasons for discontinuation were adverse events (34.6%), subject withdrawal (31.3%), lost to follow-up (12.6%). When stratified by previous treatment (*de novo* subjects, rollovers from A302 on DRF or DMF), discontinuations following AEs were highest in the *de novo* group (40%) and lower in DRF and DMF rollovers (33.3% and 24.1%). In Study A302, 94.8% of subjects completed the study, with a slightly higher discontinuation rate in the DMF as compared with the DRF group (7.2% vs. 3.2%). The most common reason for study discontinuation for both treatment groups was adverse events (DRF group: 1.6%; DMF group: 6.0% of subjects).

In the Tecfidera Pool A, discontinuation rates were similar across treatment groups (25 to 33%) and main reasons were consent withdrawn, "other," MS relapse (in the placebo group), and AEs being the most common reason for treatment discontinuations in the DMF groups.

In Study 109MS303, 963 subjects (55%) discontinued study treatment with the most common reasons being consent withdrawn (17%), AEs (14%), and other reasons (12%). 974 of 1736 subjects (56%) discontinued the study. The most common reasons for study discontinuation were consent withdrawn (17%), AEs (14%), and other reasons (13%).

Regarding baseline demographics in the DRF Study A301, the median age for all subjects was 43 years old, with the median age in de novo subjects being 41 years old, while rollovers from A302 were older (median 45 years old for DRF and 44 years old for DMF rollovers). In the Tecfidera Pool A, the median age was lower as in the DRF studies (between 36 and 39 years old).

Study inclusion criteria in the DRF clinical programme allowed subjects up to 65 years old to be included while in the DMF pivotal studies, subjects up to an age of 55 years could participate. 139 of 1057 subjects (13.2%) in the DRF Study A301 were > 55 years of age. Three subjects had a baseline age of 65 years.

The gender distribution female to male (~2:1) was similar in the DRF and DMF studies as was the race distribution (the vast majority being Caucasians). However, region was different in the two study programs with US subjects being represented in almost half of the study population in the DRF programme. In the DMF Pool A, approx. 15% of subjects were from the US.

2.6.8.2. Adverse events

AEs reported in the Phase 1 and Phase 3 studies with DRF demonstrated that the safety profile is consistent with that of DMF, which has been assessed at the time of the MAA for Tecfidera.

DRF clinical studies

Across the Phase 1 studies, the percentage of subjects with TEAEs ranged from 31.0% to 94.4%. No TEAEs were severe or serious. For both groups of subjects treated with DRF in the Phase 1 studies, i.e., healthy volunteers and subjects with renal impairment, the most frequently reported TEAE was flushing and GI events. The incidence of GI events was slightly lower for DRF as compared with DMF in most of the studies. Both events were reported more frequently with higher doses administered. No significant differences in safety or tolerability were observed in healthy volunteers across different renal impairment groups.

In the Phase 3 studies A301 and A302, 88.2% and 81% of subjects overall had at least one TEAE. 61.6% and 68.7% of subjects had at least one TEAE considered by the Investigator to be related to study treatment (Table 23).

Most of the TEAEs in Studies A301 and A302 were mild or moderate in severity. Severe TEAEs, serious adverse events (SAEs) and TEAEs that led to discontinuation of study treatment were infrequent but were reported more frequently in patients in Study A301. Regarding the two treatment groups in A302, SAEs occurred in a similar percentage in both groups, whereas all other TEAE categories were more frequently reported in patients on DMF as compared to DRF.

Table 23: Overview of AEs in the Phase 3 studies in subjects with RRMS (Safety Population)

Category	Study A301 (01 September 2020)				Study A302		
	De Novo N = 593 n (%)	**Rollover DRF N = 239 n (%)**	**Rollover DMF N = 225 n (%)**	**Total N = 1057 n (%)**	**DRF N = 253 n (%)**	**DMF N = 251 n (%)**	**Total N = 504 n (%)**
Any TEAE	519 (87.5)	210 (87.9)	203 (90.2)	932 (88.2)	198 (78.3)	210 (83.7)	408 (81.0)
Severe TEAE	52 (8.8)	23 (9.6)	23 (10.2)	98 (9.3)	5 (2.0)	14 (5.6)	19 (3.8)
Related TEAE	387 (65.3)	133 (55.6)	131 (58.2)	651 (61.6)	165 (65.2)	181 (72.1)	346 (68.7)
AE leading to discontinuation	49 (8.3)	23 (9.6)	13 (5.8)	85 (8.0)	4 (1.6)	15 (6.0)	19 (3.8)
Any SAE	69 (11.6)	28 (11.7)	23 (10.2)	120 (11.4)	4 (1.6)	3 (1.2)	7 (1.4)
Related SAE	4 (0.7)	2 (0.8)	4 (1.8)	10 (0.9)	0	0	0
Death	3 (0.5)	1 (0.4)	0	4 (0.4)	0	0	0

The most common TEAEs in Study A301 (> 10% in the overall population) were flushing (27.2%), MS relapse (19%), upper respiratory tract infection (14.3%), nasopharyngitis (12.9%), lymphopenia (11.2%), and diarrhoea (10.3%).

Most TEAEs in Study A301 were mild (29%) or moderate (49.9%) in severity, and 9.3% of TEAEs were severe, with the most frequently (in more than 5 subjects) being MS relapse, back pain, flushing, and fatigue.

61.6% of subjects had treatment-related TEAEs. Flushing was the most frequently reported treatment-related TEAE (26.9%), followed by lymphopenia (10.8%), diarrhoea (7.5%), and pruritus (5.0%).

The overall incidence of *flushing and flushing-related AEs* in Study A301 was 37.2%, mainly reported as mild to moderate in severity, and more subjects reported such events in the *de novo* group (49.2%) compared to rollovers (22.2% and 21.3% of subjects in the DRF and DMF rollover groups, respectively). The difference is due to previous treatment with DRF or DMF in rollovers during A302, in line with the timely course of these events, i.e. onset during the first month of treatment followed by a decrease thereafter. The median duration was 12.0 days (1 to 679 days). Less than 1% of patients reported severe flushing/ flushing-related TEAEs or had their dose either reduced or temporarily interrupted (all in the *de novo* group) or discontinued due to flushing or flushing-related AEs.

31.6% of all subjects had AEs in the System Organ Class (SOC) of gastrointestinal disorders with the most commonly reported (≥ 5% of subjects in any group) AEs being diarrhoea (10.3%), nausea (6.8%), constipation (4.4%), and abdominal pain upper (3.7%). The incidence of diarrhoea and nausea was slightly higher in the *de novo* group (11.1% and 7.6% of subjects, respectively) than in the DRF rollover group (7.5% and 5.0% of subjects, respectively), and it was 11.1% and 6.7% in the DMF rollover group. Overall, 1.8% of subjects had severe GI events in the GI disorders SOC. The incidence of GI events was highest during the first month of treatment. The outcome of GI events in a majority of these subjects was recovered/resolved. Median duration of these events ranged from approximately 4.5 to 6 days across the three groups. Three subjects (0.3%) discontinued study treatment due to TEAEs of diarrhoea. 1.8% of subjects had their dose reduced or interrupted temporarily due to either diarrhoea, nausea, or other GI TEAEs.

In Study A302, the most common TEAEs (≥ 10% of patients overall) with DRF and DMF were flushing (32.8% and 40.6%), diarrhoea (15.4% and 22.3%), nausea (14.6% and 20.7%), and abdominal pain upper (6.7% and 15.5%). Most TEAEs in study A302 were mild or moderate in severity. 68.7% of patients had treatment-related TEAEs, and these were mainly events of flushing, diarrhoea, nausea, and abdominal pain upper.

Flushing and flushing-related AEs combined were reported in 50.4% of subjects overall, 45.8% in the DRF group and 55% of subjects in the DMF group. No subjects in either treatment group discontinued the study drug as a result of flushing or flushing-related AEs. The median time to onset of flushing and related events was 1 day, and the median duration was 2 days.

Study A302 was a direct comparison of the effects of DRF and DMF on GI tolerability. Gastrointestinal disorders TEAEs were reported by 41.9% of subjects (34.8% on DRF and 49% on DMF). The incidence of diarrhoea, nausea, abdominal pain upper, abdominal pain, and vomiting was lower in the DRF than in the DMF group. Severe AEs were reported by three subjects in the DRF group and six subjects in the DMF group. GI TEAEs resulted in study discontinuation in 2.8% of subjects (0.8% in the DRF group and 4.8% in the DMF group). The time to onset of GI events was generally within the first two weeks of treatment in both groups, and mean duration for the most common GI TEAEs was up to seven days. Given that no significant difference on GI tolerability with DRF over DMF can be claimed, information in Section 4.8 relies on the pivotal DMF experience. ADR data from Study A302 on GI tolerability has been summarised in the SmPC Section 5.1.

The applicant presented justification for not presenting tabulated adverse drug reaction data separately for DRF and DMF owing to their similar safety profiles. It is concurred with the applicant that the design of the DRF studies is not adequate per se to evaluate frequencies of ADRs given that A302 is short-term and only active-controlled and A301 is an uncontrolled, open-label trial. Comparison between TEAEs in A301 (in ≥5% of subjects) and TEAEs in the DMF pivotal studies demonstrated that frequency categories of the ADRs defined in the Tecfidera SmPC broadly complied with those observed for DRF in study A301. For some ADRs determined for Tecfidera, the frequencies with DRF were lower (e.g. nausea, abdominal pain upper, abdominal pain, vomiting, dyspepsia, hot flush, albumin urine present, AST increased, and rash). Thus, the approach to rely on the ADR frequencies with Tecfidera is considered conservative and acceptable.

Section 4.2 of the SmPC indicates that Vumerity can be taken with or without food (with reference to Section 5.2) given that the study protocol of Study A302 allowed both situations. Upon request and in line with Tecfidera, the applicant added wording in order to indicate that food might improve tolerability of DRF in subjects experiencing flushing or GI adverse reactions.

Upon request, presentation of incidences of AEs with DRF concerning Sections 4.8 and 5.1 in the SmPC has been brought in line with that of Tecfidera in that percentages are expressed based on TEAEs.

DMF pivotal studies

For details on common adverse events with DMF it is referred to the Tecfidera EPAR (EMEA/H/C/002601/0000/Rev 1).

Common adverse events were reported in a similar number across treatment groups (87-95%; Pool A). Significant differences in the incidences of common adverse events between groups were seen for flushing (including flushing-related events (9% placebo vs. 45% DMF BID), and GI disorders TEAEs (31% placebo vs. 40% DMF BID).

Treatment-related AEs frequently derived from the vascular disorders SOC, GI disorders SOC, and skin and subcutaneous tissue disorders SOC.

In DMF Pools A and B, flushing and flushing-related symptoms, GI events, as well as increases in ALT were found to occur frequently during the first 1 to 3 months of treatment. The majority of TEAEs with DMF were mild to moderate in severity. The most common severe TEAE reported was MS relapse (5% placebo, 3% DMF BID).

In Pool A, AEs reported at an increased incidence (≥ 2%) in patients treated with DMF BID compared to placebo were flushing and hot flush, GI events (e.g., 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. There was no clear dose-relation for most of the events except for GI events.

ADRs with DMF have been defined:

- based on the differences in incidences (≥ 2%) for TEAEs between DMF 240 mg BID and placebo in the two pivotal trials, i.e., flushing and hot flush, GI events (diarrhoea, nausea, abdominal pain upper, abdominal pain, vomiting, dyspepsia), skin events (pruritus, rash, and erythema), albumin urine present, aspartate aminotransferase (AST) increased, and lymphopenia; and
- based on the mode of action of DMF lacking the 2% difference criterion, i.e. gastroenteritis, leukopenia, burning sensation, gastritis, GI disorder, proteinuria, feeling hot, alanine aminotransferase (ALT) increased, white blood cell (WBC) count decreased, and leukopenia.

DMF long-term clinical Study 109MS303

In Study 109MS303, no new safety findings could be identified with long-term DMF treatment.

94% of all DMF-treated subjects reported TEAEs, and these were mainly rated as moderate in severity. Severe AEs were reported by 21% of subjects with the most frequently severe AE being MS relapse (4%). 29% had a TEAE that was rated as related to study treatment.

TEAEs most frequently reported were MS relapse (between 30% and 42% across treatment groups), nasopharyngitis (between 17% and 31% across treatment groups), urinary tract infection (between 14% and 25% across treatment groups), and flushing (between 12% and 33% across treatment groups). TEAEs often reported as treatment-related were flushing, diarrhoea, and upper abdominal pain. Overall, reporting of flushing decreased as compared to phase 3 pivotal DMF studies. No increased incidence of events related to GI tolerability was noted with long-term treatment (35% of patients reported GI events).

Adverse events of special interest

AESIs were defined primarily based on the established safety profile, known important risks of DMF in MS patients, and nonclinical data relevant to safety for DRF and DMF, i.e,. Anaphylaxis/angioedema, Opportunistic infections, All serious infections, Lymphopenia, Liver injury, Malignancies and premalignant conditions, Renal injury, Cardiac disorders, Pancreatitis, and GI tolerability.

Anaphylaxis and angioedema as well as events of *pancreatitis* were neither reported in Study A302 nor in Study A301.

Opportunistic infections/ all serious infections

The RMP of DRF (in line with DMF) lists PML as an important identified risk and serious and opportunistic infections (other than PML and herpes zoster) as important potential risk.

No events of opportunistic infections and serious infections were reported with DRF and DMF in Study A302.

In Study A301, lymphocyte counts were closely monitored to mitigate the risk for life-threatening infections (including PML).

0.6% of subjects reported opportunistic infections (oral candidiasis, three subjects; vulvovaginal candidiasis, two subjects; candida infection, two subjects; oesophageal candidiasis, one subject); one subject had both OIs of oral candidiasis and candida infection, and one subject had both OIs of oesophageal candidiasis and candida infection. OIs were mild (four subjects) or moderate (two subjects), not serious or associated with lymphopenia, and rated not related to study treatment, except for the

TEAEs of oral candidiasis and candida infection; all but the TEAE of candida infection resolved by the cut-off date.

0.9% of subjects reported AEs associated with serious infections; two subjects with appendicitis and one subject each with cellulitis, urinary tract infection, chronic gastritis, pharyngitis, pneumonia bacterial, pneumonia, and sepsis. None of the AEs except for the fatal and serious TEAE of pneumonia bacterial led to discontinuation from the study, and all but the AE of pharyngitis were assessed as not related to study treatment. These events were not found to be related to severe prolonged lymphocytopenia. However, a relation cannot be excluded given that ALC < $0.5x10^9$/L persisting for > 4 weeks led to discontinuation from treatment.

Although not being a designated serious infection, 22 subjects (2.1%) have been identified with mild to moderate Herpes Zoster and one subject with varicella zoster virus infection in A301. Herpes Zoster is a known risk with Tecfidera treatment and labelled in the product information.

Infections were a designated AESI in the pivotal DMF clinical studies: Pool A showed slightly higher rates for infections in DMF-treated subjects compared to placebo (56% placebo vs. 60% DMF BID). Events that occurred at an incidence ≥ 2% higher in the DMF BID group compared to placebo were nasopharyngitis (20% placebo vs. 22% DMF BID), UTI (11% vs. 14%), and URTI (11% vs. 13%). Most events were mild to moderate in severity with severe events similarly reported in placebo- and DMF treated subjects. No increase in the incidence or change in the pattern of infections was observed when evaluating infections by three-month intervals. Serious infections were reported in 2% of DMF BID-treated subjects (vs. 1% on placebo), the most common being gastroenteritis (< 1% on DMF). Incidences of infections were found similar in placebo and DMF BID-treated patients across post-baseline lymphocyte count groups. No serious infections were reported in DMF-treated subjects with a minimum post-baseline lymphocyte count < 0.5 x 10^9/L or a WBC count < 3.0 x 10^9/L. No increased incidence of serious infections was observed in DMF-treated subjects with lymphocyte counts ≥ 0.5 to < 0.8 x 10^9/L compared with either placebo overall or DMF-treated subjects, who had higher lymphocyte counts.

No opportunistic infections were reported for subjects on DMF in Pool A.

Lymphopenia (incl. lymphopenia and lymphocyte count decreased)

Decreases in leukocyte and lymphocyte counts are listed as important identified risk in the RMP for DRF in line with DMF.

In the DRF clinical studies, there were no SAE reports of lymphopenia or lymphocyte count decreased, and there were no infections associated with lymphopenia or lymphocyte count decreased.

In A301, 16.7% of subjects (n=177) had TEAEs in the lymphopenia category (i.e., lymphopenia and lymphocyte count decreased) with a higher incidence in the rollover groups compared with the de novo group. Most events were mild or moderate in severity and rated as severe in six subjects; the majority of TEAEs was assessed as related to DRF. The incidence of the first occurrence of these events was highest at ≥ 3 months to < 6 months and at ≥ 12 months to < 18 months of exposure (4.1% and 4.3%, respectively). More than half of the events were resolved by the clinical cut-off date. The mean (SD) durations of lymphopenia and lymphocyte count decreased were 169.7 (176.00) and 170.4 (206.26) days, respectively. Treatment-emergent lymphopenia and lymphocyte count decreased AEs led to treatment interruption in 2.6% (28/1057) of patients. 2.1% (22 subjects) discontinued study treatment due to lymphopenia TEAEs.

In Study A302, 0.8% of subjects (n=4) reported an AESI associated with lymphopenia; one subject on DRF and three subjects on DMF; all of the events were mild in severity. The subject in the DRF group experienced lymphopenia (ALC 0.63 x 10^9/L) and reported a concomitant non-serious AE of upper respiratory tract infection assessed as not related to study drug. Both events resolved by the end of the

study with a lymphocyte count of 1.44 x 10^9/L. One subject in the DMF group had a lymphocyte count of 0.75 x 10^9/L at the time of the AE, later rising to a peak of 0.82 x 10^9/L, and reported a concomitant AE of MS relapse. Two other subjects in the DMF group had lymphocyte counts of 0.80 x 10^9/L and 0.45 x 10^9/L at the time of the AE, with no concomitant infection. Dose remained unchanged in these subjects.

Malignancies and pre-malignant conditions

DRF in line with DMF bears the risk for inducing malignancies with longer treatment duration, as it is an immunomodulatory therapy.

There were no reports of malignancies or premalignant events in Study A302.

In *Study A301,* 0.5% of subjects (n=5) reported malignancies (basal cell carcinoma, Bowen's disease (squamous cell carcinoma), diffuse large B-cell lymphoma, invasive ductal breast carcinoma, and malignant melanoma). 0.7% of patients (n=7) reported premalignant conditions (endometrial hyperplasia (3 patients), cervical dysplasia, dysplastic naevus, large intestine polyp, laryngeal dysplasia, and leucoplakia).

The incidence of malignancies was similar to that in the controlled Tecfidera clinical programme. In Pool A, the incidence of malignancies was low and balanced (< 1% [three subjects] placebo, < 1% [two subjects] DMF- BID, <1% [two subjects] DMF TID, 1% [four subjects] GA). Malignancies included breast cancer, basal cell skin carcinoma, and breast neoplasm in the placebo group; transitional cell carcinoma of renal pelvis and basal cell skin carcinoma in the DMF BID group; breast cancer and cervix cancer in the DMF TID group; and cervix cancer, endometrial cancer, thyroid cancer, and basal cell skin carcinoma in the GA group. One case of breast cancer was reported in a subject treated with DMF for 11 months during Study C-1900.

The long-term risk for malignancies with DMF treatment has been further assessed in Study 109MS303, with the overall incidence being 3% and the lack of a specific malignancy pattern. Additional analyses on malignancies and background rates have been requested in the ongoing variation EMEA/H/C/002601/II/0069/G with focus on skin cancers, which should be addressed in the upcoming PSUR (submission date 24 June 2021). This procedure is ongoing (EMEA/H/C/PSUSA/00010143/202103) at the time of this assessment. Depending on the outcome, amendments to the product information might become necessary, which would then also be relevant for the DRF product information. The applicant's request to remove malignancies from the list of potential risks associated with Tecfidera in the RMP was not deemed acceptable until results from the observational Study 109MS401 (a PASS study) become available.

Liver injury

Drug-induced liver injury (DILI) is an important identified risk with DRF in line with DMF in the respective RMPs.

TEAEs of increases in liver transaminases were reported in Phase 3 studies A301 and A302. None of these increases were associated with increases in bilirubin (no reports of Hy's law). The incidence of liver injury AESIs was low across groups in both studies. Less than 1% of all DRF–treated patients in either study had liver function tests > 5x ULN or > 10x upper limit normal (ULN).

In *study A301*, TEAEs in the liver injury category were reported in 7.2% of subjects. The most commonly reported liver injury events were ALT increased (5.5%) and AST increased (2.9%). All other events (Preferred Terms [PTs]: liver function tests (LFT) increased, blood bilirubin increased, hepatic enzyme increased, blood ALP increased, transaminases increased, urobilinogen urine increased, cholestatic liver injury, hepatic steatosis, and hepatosplenomegaly) were each reported in ≤ 0.5% of subjects.

The mean (SD) time to onset of events was 139.1 (186.65) days (median: 30 days), with a majority of them having occurred in the first six months of treatment. Most of the TEAEs in the liver injury category were mild or moderate, and the majority (82.9% of patients) resolved. Liver injury events were assessed as related to DRF in a majority of subjects. Seven subjects had AEs related liver function parameters leading to treatment discontinuation. Three TEAEs (LFT increased, ALT increased, and cholestatic liver injury) were assessed as serious. For SAEs of LFT increased and ALT increased, study treatment was withdrawn, and the events resolved. The SAE of cholestatic liver injury resolved with sequelae.

In *Study A302*, 5.4% of subjects reported at least 1 TEAE in the liver injury AESI category, with a similar incidence in the two treatment groups (DRF 5.9% and DMF 4.8%). The most frequently reported TEAEs were ALT increased (4.6% of all subjects) and AST increased (2.8% of all subjects); the majority of the events were mild or moderate in severity. Two severe TEAEs of ALT increased were reported, each by one subject in the DRF and in the DMF group, and two severe TEAEs of AST increased were reported, both by subjects in the DRF group. The majority of liver injury events were considered possibly, probably, or definitely related to treatment by the Investigator, and approximately half of the events remained unresolved by the end of the study. There were no discontinuations due to events of liver injury, and none of the events was serious.

The incidences and the time course for liver injury AESI for DRF are basically in line with results for hepatic disorder events reported in DMF clinical Pools A and B. In Pool A, the incidence of hepatic TEAEs was similar across treatment groups (9% placebo vs. 9% DMF BID and 10% DMF TID) and headed by elevations of liver transaminases. These were ALT increased (5% placebo vs. 6% DMF BID and TID), AST increased (2% placebo vs. 4% DMF BID and TID), gamma-glutamyltransferase (GGT) increased (2% placebo vs. 3% DMF BID and 2% DMF TID), and hepatic enzyme increased (1% placebo vs. <1% DMF BID and 1% DMF TID). Serious hepatic AEs were reported for two placebo-treated patients (hepatic enzyme increased), in one female subject (cholestatic hepatitis), and in another unspecified subject (cholelithiasis) both receiving DMF BID. Hepatic events leading to treatment discontinuation were low (<1%) and similar in all groups.

To conclude, the risk of liver injury in patients treated with DRF is in line with DMF. Adequate wording has been implemented in the SmPC in line with Tecfidera.

Renal injury

The kidney was identified as the target organ of DMF toxicity from the DMF nonclinical programme. Renal findings from the DRF nonclinical programme are consistent with those observed in the DMF nonclinical programme. Proteinuria is a common ADR with DMF and likewise included in Section 4.8 of the DRF SmPC.

In *Study A301,* 7.8% of subjects had TEAEs from the renal and urinary disorders SOC.

Mild or moderate, non-serious AEs within the renal injury AESI category were experienced by 3.4% (36/1057) of subjects, with proteinuria being the most common event (1.3%), followed by haematuria (0.9%), and GFR decreased (0.9%). The majority of the events were assessed as not related to DRF (in 19 of 36 subjects). No serious or fatal renal injury events were reported. One AE each of glomerular filtration rate decreased and renal impairment resulted in study discontinuation. The mean (SD) time to onset of the renal injury events in Study A301 was 249.4 days (224.15 days). The time to onset of the TEAEs in the renal injury AESI category varied with a majority being reported within 12 months of treatment start. At the clinical cut-off date, renal injury events were reported as resolved in a majority of subjects (29 of 36).

In *Study A302, a* total of 1.6% (8/504) of subjects reported at least one AE in the renal injury category with similar incidence between the DRF and DMF groups (1.2% and 2%), headed by proteinuria (0.8% and 1.2%), haematuria (one subject in each group; 0.4%), and albumin urine present (one subject in

the DMF group). The events of proteinuria were mild in severity; were considered by the Investigator as definitely not (1 event), possibly (2 events), or probably (2 events) related to treatment; and 4 of 5 events were not resolved by the end of the study. None of these AESIs was serious or led to study discontinuation.

In the *DMF clinical programme*, the incidences of AEs belonging to renal and urinary disorders SOC in Pool A were similar in DMF-treated subjects compared to placebo (18% placebo vs. 19% DMF BID and 22% DMF TID). The most common TEAEs were proteinuria (placebo 7% and DMF BID 9%), haematuria (placebo 4% and DMF BID 4%), microalbuminuria (placebo 3% and DMF BID 5%), and albumin urine present (3% placebo and 6% DMF BID). The latter is a "common" ADR for DMF and likewise included in the SmPC for DRF. Most of the events were rated as mild or moderate in severity, were dose-related, and resolved. Treatment discontinuations due to these events were low (< 1% in all groups). The incidence of serious renal and urinary TEAEs was low (< 1% in all groups), and no serious AE of renal failure was reported.

Subjects in the DMF Phase 3 studies, who developed pre-specified abnormal urine laboratory values were examined by a nephrologist (16% placebo vs. 20% DMF BID and TID, 21% GA). Most of the subjects did not have a renal dysfunction prior to dosing (93% to 96% across groups). No DMF-treated subject had new or worsening renal function post-dosing. There was no evidence of drug-induced nephrotoxicity in DMF-treated subjects according to the nephrologist consultation.

However, results of a subgroup analysis within the placebo-controlled DMF studies demonstrated an increased incidence of renal and urinary AEs (primarily proteinuria) in subjects with concomitant potentially nephrotoxic medication compared with subjects without such medication. Therefore, interaction with nephrotoxic medications leading to renal toxicity is listed as an important potential risk in the RMP for DRF in line with DMF.

A review of laboratory data in Pool A revealed no notable differences between the placebo and DMF groups in any kidney function test. Urinalysis results and urinary β2-microglobulin or microalbumin results were likewise not significantly different between DMF and placebo (see section "Laboratory findings"). Moreover, subjects who continued on DMF for more than two years in Pool B had no clinically relevant changes in renal function tests or urinalyses and no worsening/ progression in β2-microglobulin or microalbumin.

Cardiac disorders

Cardiac disorders were considered an AESI because of findings of myocardial infarction with fumaric acid esters as well as nonclinical (rat) cardiac findings of necrosis and inflammation for DRF, which are rather considered a rat-specific finding (reference is made to the nonclinical part of this document). Subjects with significant cardiovascular conditions were excluded from the DRF and DMF clinical studies.

In the Phase 1 studies, cardiac disorder TEAEs were mainly palpitations and extrasystoles. In addition, events of presyncope, tachycardia, sinus tachycardia, and dizziness (only in DMF groups) were reported. No new concern is to be raised from healthy volunteer studies with DRF.

In Study A301, 6% of subjects were included despite having a medical history of cardiac disorders.

In *Study A301,* 13.4% (142/1057) of subjects experienced AEs within the cardiac disorders AESI category with a slightly higher reporting in the DMF rollover group (16.9%) than in the de novo and DRF rollover groups (11.8% and 14.2%, respectively). Most AESIs were mild or moderate, 0.6% of subjects reported severe AESIs. The majority (63.4%) had an outcome of recovered/resolved with continued treatment.

Nonspecific dizziness was the most frequently reported event (by 5.4% of subjects). Other cardiac disorder events included oedema peripheral (1.5%), dyspnoea (1.2%), syncope (0.9%), chest

discomfort and tachycardia (0.8% each), palpitations (0.7%), atrioventricular block first degree (0.7%), and chest pain and peripheral swelling (0.5% each). One event each of hypertensive heart disease and cardiac arrest with fatal outcome were assessed as severe SAEs and not related to study treatment (see section on "deaths" in this report). Other SAEs reported in the cardiac disorders category were ventricular extrasystoles, cardiac failure, stress cardiomyopathy, and myocardial infarction; all these SAEs were assessed as not related to study treatment and had an outcome of resolved/recovered at the time of the data cut-off. One event each of cardiac arrest, dyspnoea, and myocardial infarction led to study treatment discontinuation.

In *Study A302,* AESI in the cardiac disorders category were reported in 3.0% (15/504) of subjects with similar incidences in both groups (DRF: 2.8%, DMF: 3.2%). The most common cardiac disorder AE was dizziness (in 1.4% of total subjects, 2.0% on DRF and 0.8% on DMF). All other TEAEs were reported in single subjects only. None of the cardiac disorder-related AESIs led to study discontinuation. Most events in both groups were mild (DRF group) or mild to moderate (DMF group). One event of atrial fibrillation was a SAE (rated as probably not related to DRF). One subject in the DRF group interrupted treatment due to an event of pulmonary congestion (probably not related to DRF).

In the *DMF clinical studies*, incidences for cardiac disorder events were similar for all treatment groups (5% to 6%). Incidences for ischemic CV events were small and similar across groups (≤ 1%). Serious cardiac disorder events were not reported for placebo or DMF BID. Pooled analysis using pivotal DMF studies 109MS301 and 109MS302 to further investigate the risk of cardiovascular events under DMF treatment in relation to existing cardiovascular risk factors at baseline did not reveal a higher risk in patients treated with DMF compared to placebo. The overall numbers of events were similar in all treatment and dosing groups except for a slightly higher AE rate for tachycardia and palpitations in subjects with risk factors at baseline. In addition, ECG changes were low and similar in all treatment groups. In the extension Study 109MS303 (up to 12 years of treatment with DMF), 23 subjects (1%) had an ischemic cardiovascular disorder event.

Gastrointestinal tolerability events

The GI tolerability AESI category in DRF Phase 3 studies included only those events among specified search criteria that were SAEs and TEAEs leading to study treatment discontinuation.

In *study A301*, GI-related TEAEs were among the most commonly reported TEAEs (31.6%), but GI SAEs (ten subjects, 0.9%) and GI events leading to study discontinuation (seven subjects, 0.7%) occurred in few subjects only. eight of the 17 subjects with SAEs and AEDC captured in the GI disorders SOC (five subjects with SAEs and three subjects with AEDCs) met the specified search criteria for AESI (0.8% of all subjects). Abdominal pain and diarrhoea were reported in three subjects each, followed by gastritis (two subjects), and chronic gastritis and vomiting (one subject each). Time to onset of the TEAEs in the GI tolerability category varied substantially (ranging from 4 days to 547 days); in six of eight subjects, GI events were reported within the first nine months of treatment. TEAEs associated with GI tolerability were mild and moderate in one and four subjects, respectively, and severe in three subjects, and all were recovered/resolved by the data cut-off. All but one (one subject with vomiting and abdominal pain) GI tolerability events were assessed as related to DRF.

In *Study A302*, a direct comparison of GI tolerability in patients treated with either DRF or DMF was the primary objective. A total of 2.8% (14/504) of subjects reported at least one GI tolerability AESI, 4.8% of subjects in the DMF group, and 0.8% of subjects in the DRF group. None of these AESIs were SAEs, but all led to study discontinuation, and most of them were mild or moderate in severity. The three severe events (two events of abdominal pain and one event of abdominal pain upper) all occurred in the DMF group. The two AESI of GI tolerability in the DRF group were diarrhoea and vomiting, which were mild and moderate in intensity and related to DRF. In the DMF group, abdominal pain upper was the leading cause of discontinuation (2.0% of patients). The majority of these events were mild or moderate

in severity and considered as related to the treatment. The outcome of all events was considered recovered/resolved. Other GI AESIs leading to discontinuation experienced by ≥ 2 subjects in the DMF group included diarrhoea, abdominal pain, and vomiting.

In the DMF Pool A, TEAEs associated with GI tolerability in DMF-treated subjects were more frequently reported compared with placebo (40% DMF BID vs. 31% placebo). Frequently reported PTs were diarrhoea, nausea, abdominal pain upper, abdominal pain, and vomiting. GI disorders leading to treatment discontinuations were reported in 4% and 6% of patients in the DMF BID and TID group. The time course for GI tolerability events was highest during the first month and declined during the second month and thereafter. Serious GI AEs (most common vomiting, abdominal pain, and gastritis) were reported in up to 1% of subjects across treatment groups.

Data on gastrointestinal tolerability with DRF do not indicate relevant differences compared to those reported in the pivotal DMF clinical studies. The results of the primary endpoint analysis are considered debatable given that these are based on GI scales that have not been validated, the choice of the endpoint is questionable and an anticipated lack of statistical robustness. As such, referencing product-specific data on DRF in Section 4.8 is dispensable and information should rely on the Tecfidera pivotal experience, which is considered conservative. Upon discussion of the mechanism underlying the proposed increase in GI tolerability of DRF compared with DMF, there is no evidence to support that any of the presented mechanisms (i.e. the lower concentration of methanol formed, the larger particle size of DRF limiting binding to receptors within the gastrointestinal tract, and the lower electrophilicity of DRF) are important in the hypothesised better tolerance of DRF.

2.6.8.3. Serious adverse event/deaths/other significant events

Deaths:

In the DRF programme, four SAEs with fatal outcome were reported, all of which occurred in Study A301 as of the clinical cut-off date. Three events occurred in *de novo* subjects:

- fall in a subject (age 20 to30 years) with DRF for 213 days and no relevant medical history was assessed as not related to DRF; the conditions that led to the subject's death were shock and multiple bone fractures with internal organ damage, intention unspecified.

- "hypertensive heart disease" with fatal outcome in a subject (age 50 to 60 years) with DRF for > 250 days and relevant medical history, including hyperlipidaemia, asthma, and hypertension was assessed as not related to DRF.

- "pneumonia bacterial" in a subject (age 30 to 40 years) with DRF for > 500 days without relevant medical history that led to acute respiratory failure and the subject's death, which was assessed as not related to DRF. No other relevant abnormalities were reported.

One subject (40 to 50 years) with DRF for > 75 days in the DRF rollover group died from a cardiac arrest (assessed as probably not related to DRF) without relevant medical history or other confounding factors. ECG parameters obtained before the fatal event (in A302 and in A301) were unremarkable.

A total of 16 deaths have been reported in the DMF clinical development programme with seven of them reported at the time of MAA submission of Tecfidera (cut off 03 August 2011). Five deaths belonged to the DMF groups, one to the placebo group (ischemic stroke), and one to the GA group (suicide).

The five deaths in subjects on DMF occurred due to a traumatic brain injury from a bicycle accident, a road traffic accident, complications of an MS relapse (in the controlled studies), a MS relapse and cardiopulmonary arrest related to paraplegia and respiratory muscle weakness, and suicide (both in the

uncontrolled Study 109MS303). None of these deaths was considered related to treatment with dimethyl fumarate.

A total of 11 deaths were reported during Study 109MS303 with nine of them between the interim (03 August 2011) and final data cut-off (08 November 2019) due to adenocarcinoma of the lung, terminal cardio respiratory arrest due to type I respiratory failure due to aspiration pneumonia, thrombotic emboli in pulmonary artery, complication MS, suicide (unlikely related), cardiac arrest, mesothelioma, aspiration pneumonia (in a patient with ongoing PML; rated as related to DMF), and malignant disease.

Serious adverse events

No SAEs were reported in any of the Phase 1 studies with DRF.

In Study A301, SAEs were reported by 11.4% (n= 120) of subjects, 11.6% in the De Novo group, and 11.7% and 10.2% in the DRF and DMF rollover group, respectively. Of the 120 subjects with SAEs, 61 had SAEs of MS relapse during the Treatment Period. The majority of cases occurred in non-US countries where MS relapse is commonly treated in a hospital setting, which defines the cases as serious. The other SAEs occurring in more than one subject were abdominal pain (three subjects), gastritis, cholecystitis, inguinal hernia, appendicitis, fall, uterine leiomyoma, suicidal ideation, and respiratory failure (two subjects each). Ten SAEs were considered related to study treatment by the Investigator (four of ten SAEs were from the GI disorders SOC).

In Study A302, SAEs were reported in a total 1.4% of subjects (1.6% of patients in the DRF group and 1.2% of subjects in the DMF group); all were assessed as not related to study treatment and were resolved or resolved with sequelae by the end of the study. In the DRF group, SAEs reported were atrial fibrillation (1 patient), MS relapse (two subjects), and MS relapse/suicide attempt (one subject); in the DMF group, SAEs reported were MS relapse (two subjects) and cholecystitis (one subject). One SAE (suicide attempt in the DRF group) led to discontinuation from the study.

SAEs in DMF studies occurred with a slightly lower incidence in DMF-treated subjects compared to placebo (16% vs. 21%). MS relapse was the most frequently mentioned SAE (9% DMF vs. 14% placebo). SAEs related to GI disorders and flushing did not exceed a 1% incidence in any treatment group. Serious flushing events occurred in a low number in DMF-treated subjects (< 1% each). Three out of 2,560 subjects in DMF clinical trials experienced serious flushing symptoms that were in line with hypersensitivity or anaphylactoid reactions. These events were not life threatening but led to hospitalisation. Cases of anaphylaxis/ anaphylactoid reaction have likewise been reported following Tecfidera administration in the post-marketing setting. The mechanism of dimethyl fumarate induced anaphylaxis is unknown. Detailed information is presented in Section 4.4 of the Tecfidera SmPC.

SAEs during the extension Study 109MS303 were reported in 551 subjects (32%). The SOCs with the highest incidence of SAEs were nervous system disorders (16%), and infections and infestations (5%). In total, the most frequent SAE by PT was MS relapse (14%). Serious treatment-related AEs occurred in 4% of subjects in the study. All treatment-related SAEs by PT occurred in less than 1% of subjects.

2.6.8.4. Laboratory findings

Haematology parameters

The predominant findings in pivotal studies with DMF were a reduction in mean leukocyte (WBC) and lymphocyte counts from baseline, roughly starting at Week 4 through Week 48, with a plateau up to Week 96 compared to placebo, but remained above lower limit of normal (LLN) at all time points. Mean reduction for WBC counts and lymphocytes was 11% and 30%, respectively, up to Week 48. There was no further worsening up to 3.5 years of treatment. Consistent with these findings, decreases in

lymphocyte and leukocyte counts starting at Week 4 through Week 48 and a plateau up to Week 96 were noted for DRF with identical mean decreases from baseline to Week 48.

Shift analyses in Study A301 confirmed these findings and were found similar to DMF clinical studies: the most common shifts (≥ 10% of subjects) from normal/high baseline to low were observed for lymphocytes (39.8% of subjects), erythrocytes (30.7% of subjects), leukocytes (27.8% of subjects), and neutrophils (16.8% of subjects). The most common shifts from normal/low baseline to high were found for neutrophils (20.7% of subjects), and leukocytes (13.8% of subjects). PCS haematology parameters of lymphocytes < 0.5 × 10^9/L, neutrophils, absolute < 1.5 × 10^9/L, and leukocytes ≤ 2.8 × 10^9/L were observed in 8.9%, 5.9%, and 7.2% of subjects.

42.4% of subjects had lymphocyte counts below LLN (< 0.91x10^9/L) and lymphopenia was mainly reported as moderate (Grade 2, in 22.6% of subjects). In 13.7% of all subjects (143 of 1045), moderate lymphopenia was prolonged for at least six months, i.e., 13.7% of de novo subjects, 16% of subjects treated with DRF and 11.1% of subjects treated with DMF. An obviously higher number of subjects with lymphopenia and moderate prolonged lymphopenia for ≥ 6 months reported in the DFR groups as compared to the DMF rollover group is not based on a biological mechanism since lymphopenia is thought to be an MMF-mediated effect. The difference might be attributed to the overall shorter treatment duration with DMF and the fact that lymphopenia does not tend to occur during the first five weeks of treatment with DMF. Grade 3 lymphopenia was experienced by 10.5% and 8.9% of subjects from the DRF and DMF group, respectively (rollover subjects). Severe prolonged lymphopenia (absolute lymphocyte count (ALC) < 0.5x10^9/L for at least six months) has not been reported in A301 given that patients with lymphocyte counts < 0.5x10^9/L for ≥ 4 weeks had to discontinue DRF according to the protocol. Follow-up LM revealed that the number of subjects with lymphopenia declined during a maximum follow-up period of six months (three LM visits). Nevertheless, at LM Visit 3, 18 subjects still had Grade 2 or 3 lymphopenia.

Analyses of pivotal DMF studies demonstrated slight recovery of lymphocytes four weeks post dose (after study treatment discontinuation or completion). Nevertheless, these data were considered inconclusive given the short follow-up period. Lymphocyte recovery after stopping DMF treatment was also evaluated in 109MS303. In subjects with ALC < LLN at recovery baseline and with ALC < 0.8x10^9/L at recovery baseline, lymphocyte recovery to ≥ LLN within the follow-up period (up to 48 weeks) was observed in more than half of these subjects. Using a linear mixed-effect model, the estimated time to reconstitution to ALC > LLN in patients with ALC < LLN was 4.7 weeks. These data did not include subjects with severe prolonged lymphopenia (i.e., ALC < 0.5x10^9/L for more than six months). A number of uncertainties have been identified for the datasets and statistical analysis underlying this evaluation (reference is made to the ongoing procedure EMEA/H/C/002601/II/0069/G). Given that lymphocyte count reconstitution data are proposed to be included in Sections 4.8 and 5.1 of the SmPCs for DMF and DRF, these discrepancies have to be solved in advance, which has been confirmed by the applicant. Until agreement on a wording, inclusion in the Vumerity SmPC seems dispensable, which has been agreed to by the applicant.

In the DMF Pool A, a transient increase in mean values for eosinophils was reported in the first 2 months of treatment with DMF. In Study A302, there were increases seen in eosinophil counts both for DMF and DRF and transient increase in mean eosinophil counts was likewise observed in de novo subjects in study A301.

There were no other clinically meaningful findings in the haematology results in Study A302.

Chemistry parameters

No clinically significant changes from baseline in chemistry parameters were noted in Phase 1 studies in healthy volunteers or in the Phase 3 Study A302.

There were no clinically meaningful mean changes from baseline in serum chemistry parameters in Study A301, including metabolic parameters, electrolytes, and creatine kinase. Laboratory parameters were not specifically taken in fasting condition; thus, variability is to be expected. Small mean increases from baseline were noted for blood calcium and sodium in all treatment groups. Individual metabolic subject changes were similar across groups and included shifts from normal/low to high in glucose and high-density lipoprotein (HDL) cholesterol, and shifts from normal/ high to low in cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides. The most frequently reported individual change in electrolytes concerned normal/ low to high potassium in 8.7% of patients. 6.0% of subjects reported a PCS change in potassium (>5.5mmol/L).

Findings were in overall accordance with those in the DMF clinical programme. Special blood chemistry tests only conducted in pivotal DMF studies included parathyroid hormone and Vitamin D levels, which were monitored in order to substantiate preclinical findings in rats with renal failure. Studies 109MS301 and 109MS302 showed increased mean parathyroid hormone levels from Week 48 to Week 96 and decreased Vitamin D levels (-20% of baseline values) in DMF-treated subjects compared to placebo. No such data are available for DRF.

Urinalysis

There were no clinically significant findings for urinalysis parameters in DRF studies, including nine Phase 1 studies in HV. In Study A108 (subjects with renal impairment), abnormal postbaseline urinalysis results were observed most frequently in the severe renal impairment group and already present at baseline. The most frequently mentioned abnormality was protein urine (37.5%).

In A301, there were no clinically relevant differences across treatment groups in patients with abnormal urinalysis parameters (urine pH, specific gravity, ketones, protein, glucose, bilirubin, nitrite, urobilinogen, occult blood, albumin/creatinine, and β2-microglobulin). Abnormal urinalysis parameters were most frequently reported for urine protein, urine ketones and urine occult blood (in 76.6%, 55.3%, and 37.4% of all subjects) and similar across treatment groups without affecting renal function. Abnormal urinalysis results did not correspond with the incidence of renal TEAEs.

A PCS abnormal value for β2-microglobulin defined as > 0.300 mg/L (early marker of renal tubular damage) was reported in 15.3% of subjects. 2.1% of patients reported a TEAE of increased ß2-microglobulin in urine. A similar percentage of subjects reported TEAEs in line with microalbumin (increase in the urine albumin/creatinine ratio; 2.8%). The incidences of these TEAEs correspond with results from ß2-microglobulin and microalbumin monitoring during DMF studies: more than 95% [85%] of subjects had ß2-microglobulin [microalbumin] values within the normal range (≤0.29 mg/L) [≤1.8 mg/dL] at baseline and subsequent time points. Subjects, whose ß2-microglobulin or microalbumin values exceeded the normal range, remained on these values throughout the study. A similar incidence of shifts to high urine β2-microglobulin was observed across the placebo, DMF BID and TID, and GA groups (9% to 10%, each group) based on pooled data from Studies 301 and 302. Shifts to high in urine microalbumin were higher in the DMF BID and TID groups (36% and 37%, respectively) when compared to placebo (29%) and GA (33%). No significant changes in β2-microglobulin and microalbumin were noted across treatment groups and over time (through 3.5 years) providing some reassurance that renal tubular damage is not an issue in the majority of DMF-treated subjects. Moreover, during the entire duration of Study 109MS303, the majority of subjects remained on normal levels of urine β-2 microglobulin and urine microalbumin.

In Study A302, abnormal urinalysis parameters and PCS abnormalities were likewise reported but with lower incidences due to the shorter treatment duration and similar across treatment groups.

In the DMF clinical programme, the percentage of subjects with two positive urinalyses for protein was lowest for placebo (47%) and highest for GA (56%), and 51% for DMF BID. There was no relevant

difference with regard to two consecutively positive findings of proteinuria on urinalysis, and in the incidence of urinalysis with 3+ or 4+ protein in the different treatment groups.

Elevated urine ketones were reported for DMF-treated subjects compared to placebo and GA: 21% DMF BID, 5% placebo, and 4% GA. Shifts to high/positive values in the DMF BID group was 63% compared to 26% placebo for urine ketones.

Liver function

In the DRF clinical Phase 1 studies, there were no clinically meaningful or numerically significant changes observed for ALT, AST, albumin, alkaline phosphatase (ALP), bilirubin, total protein, lactate dehydrogenase (LDH), or GGT in healthy volunteers or in those with renal impairment in Study A108.

In the DRF clinical Phase 3 studies, transient mean increases in liver transaminases were reported typically within the first four weeks of treatment, and in a majority of subjects, increases were in line with values of ALT and/ or AST ≤ 3x ULN. PCS abnormalities of higher degrees (i.e., > 3x ULN, > 5x ULN, and > 10x ULN) occurred in no more than 2% of subjects and - as expected - given the onset of liver enzyme increases, more pronounced in the de novo group.

Mean increases in ALT and AST in Study A302 have been observed shortly after treatment initiation up to Week 3 with a subsequent plateau up to the last assessment in the treatment period. While mean changes were almost identical for DRF and DMF, slightly more subjects on DRF than on DMF were reported to have shifts from normal/ low at baseline to high post-baseline (ALT: 25.9% vs. 16.4%; AST: 15.8% vs. 9%). However, most of the elevations were < 3x ULN; therefore, this rather small difference between groups at the expense of DRF is not considered clinically relevant. Moreover, any post-baseline abnormal liver function tests and PCS values of higher degrees for ALT and AST were found slightly higher in patients on DMF as compared to DRF. No concern is to be raised for other liver parameters, i.e. ALP, bilirubin, or LDH.

None of the patients in either DRF study experienced liver enzyme increases in line with Hy's law (total bilirubin ≥ 2x ULN and ALT or AST ≥ 3x ULN). Liver enzyme changes were also not associated with an increase in clinically significant liver disease.

In the DMF clinical programme (Pool A), hepatic transaminases ALT and AST increased in DMF BID and TID-treated subjects compared to placebo, with a peak at Week 4 with mean ALT exceeding the ULN for DMF TID. Both transaminases returned to baseline values around Week 32. ALT and AST maximum post-baseline values were in a majority of patients < 3x ULN (in more than 90% of subjects) and similar low proportions in the DMF and placebo group as well as in the GA group had values ≥ 3x ULN. Maximum post-baseline values > 10x ULN or > 20x ULN were of rare incidence (≤ 1%). Liver enzyme increases in line with Hy`s law were not reported in the DMF clinical programme.

Most subjects had maximum post-baseline total bilirubin levels of ≤ 1x ULN (90% to 93% across treatment groups) and 7% to 10% of subjects across treatment groups had values of > 1x ULN. Similar and stable values were reported for long-term treatment in Pool B.

Renal function

Renal function was regularly assessed in the DRF clinical programme.

There were no clinically meaningful changes observed in renal parameters in any of the Phase 1 studies in healthy volunteers. Two subjects from the renal impairment Phase 1 Study A108 (one from the moderate and one from the severe impairment cohort) were reported with PCS high BUN (> 30 mg/dL) and with PCS high BUN (> 30 mg/dL) and creatinine (≥ 2 mg/dL).

There was no evidence for an impaired renal function with DRF treatment in Studies A301 and A302 based on mean renal parameter values over time for albumin, creatinine, urate, BUN or glomerular

filtration rate. Moreover, no clinically relevant results on renal function derived from shift analyses and potentially clinically significant abnormalities in the phase 3 studies and results were similar for and DMF in A302.

During the DMF clinical development programme, intensive monitoring of kidney function was undertaken. Laboratory evaluation revealed no clinically notable changes in mean values for BUN or creatinine over time for DMF BID and TID groups and no relevant differences from placebo. Mean values did not exceed normal ranges at the assessed time points across treatment groups. Shifts to high were similar and low for these analytes.

Vital signs and other observations related to safety

Evaluation of *vital sign* parameters included SBP, DBP, HR, RR, temperature, weight, and BMI.

There were no clinically meaningful findings in vital signs in the DRF clinical studies: in study A301, PCS vital sign values (i.e., systolic blood pressure, diastolic blood pressure, and heart rate) were reported in less than 2% of all subjects and similar across treatment groups. Data from Study A302 were in support of these results. There was no clinically significant difference in any of the vital signs or change in body weight described for DMF, placebo, or GA-treated subjects during the DMF clinical programme. The Tecfidera product information does not mention ADRs or warnings related to vital signs.

There was no safety issue associated with *ECG measurements* in the Phase 1 studies.

In the TQT study (Study ALK8700-A110), multiple doses of therapeutic (462 mg BID) and supratherapeutic (924 mg BID) oral DRF doses did not cause QTcF prolongation exceeding 10msec. Additionally, up to the supratherapeutic dose, DRF did not have a clinically relevant effect on heart rate, PR interval, QRS interval, T-wave morphology, or U-wave presence.

There were no clinically meaningful trends or changes from baseline for ECG measurements in subjects treated with DRF in A301 or within or between DRF or DMF treatment groups for ECG measurements in A302. TEAEs related to ECG findings in A301 were reported in few subjects only with the most frequently mentioned TEAEs being tachycardia (0.8%), palpitations (0.7%), AV block first degree (0.7%), ventricular extrasystoles (0.4%), and bundle branch block right (0.3%). The events of cardiac arrest, cardiac failure, myocardial infarction, stress cardiomyopathy, ventricular extrasystoles, and hypertensive heart disease were considered SAEs. The event of hypertensive heart disease in a patient with a number of medical conditions (including hypercholesterolemia) was fatal and was judged definitely not related to study treatment.

During the DMF clinical programme, ECGs were performed at baseline and at 12-week intervals through Week 48 in Study C-1900, and at baseline and every 24 weeks in Studies 109MS301 and 109MS302. There were no relevant changes in QTc interval or any other quantitative or qualitative ECG parameters.

Suicidality assessments (C-SSRS) were included in DRF studies because the compound is administered to a patient population with a neurologic disorder with an increased prevalence of depression and an elevated risk of suicide. Data from the DRF clinical programme do not indicate an increased risk for suicidality with DRF (or DMF) treatment. Single events of suicidal ideation were reported in study A302 in both treatment groups post-baseline and one subject in the DRF group with relevant medical history experienced a SAE of suicide attempt. In Study A301, an increase of suicidal ideation post-baseline over baseline was reported (2.1% vs. 0.2%), which is considered an effect of longer treatment duration in a population with an increased prevalence of depression.

No risk on an increased rate for depression or suicidality was detected in the DMF clinical programme; however, no dedicated suicidality assessment was implemented. Adverse events contributing to depression, suicidal ideation, suicide attempt, completed suicide etc. occurred in a low and similar incidence across different treatment groups in DMF Pool A. There was a slight increase in depression for

DMF-treated subjects in Pool B (2% placebo vs. 7% DMF BID). Serious adverse events with respect to depression and suicidal tendencies were rare and balanced across groups.

2.6.8.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.6.8.6. Safety in special populations

No dedicated DRF clinical study has been performed in special populations with MS.

Patients with significant cardiovascular, pulmonary, gastrointestinal, dermatologic, psychiatric, neurologic (other than MS), endocrine, renal or hepatic conditions, and/ or other major disease were excluded from the clinical trials.

The incidence, severity, and relationship to DRF treatment of TEAEs were similar overall and across treatment groups when analysed by intrinsic (Study A301) and extrinsic factors (Studies A301 and A302).

No patient was younger than 18 years or older than 65 years of age at the time of inclusion in the DRF Phase 3 studies. The mean (SD) age of subjects was 42.5 (10.78) years old, with 59.6% being ⩾ 40 years of age. Age did not affect the incidence of TEAEs between the two age groups: TEAEs were reported by 88.9% of subjects ⩾ 40 years of age and by 84.8% of subjects < 40 years of age. The incidence of TEAEs leading to discontinuation of study treatment was slightly higher in subjects ⩾ 40 years of age compared to subjects < 40 years of age (9.2% vs. 4.7%). Upon request, data has been provided on the safety profile in patients ⩾ 55 years vs. younger patients, which is considered a relevant information given that the applicant claims an age cut-off of 65 years in Section 4.2 of the SmPC (reference is made to ”Patient exposure”). The overall safety profile in subjects treated with DRF and aged < 55 years is generally found in line with that in patients aged ⩾ 55 years, with adequate wording in place in Section 4.2 of the SmPC. Strikingly, subjects with lymphopenia TEAEs and those having discontinued DRF due to lymphopenia were found twice as high in the older subgroup. This is in line with scientific literature discussed during variation procedure EMEA/H/C/2601/II/63: *Longbrake and co-workers (Longbrake EE et al. Mult Scler J Exp Transl Clin. 2015*) found that more than 40% of subjects above 55 years of age develop Grade 2 or 3 lymphocytopenia (probably related to immunosenescence). Due to the applied inclusion criteria in the Tecfidera studies, this relation has not and could not be observed. Therefore, it cannot be ruled out that general immunosenescence at advanced age could lead to a higher susceptibility for opportunistic infections in MS patients >50 years.

Regarding race, no meaningful conclusions can be drawn given that 92.0% of patients were of Caucasian origin.

Otherwise healthy volunteers with no, mild, moderate, and severe renal impairment were studied in a single-dose Phase 1 study (A108). Renal impairment had no effect on the PK exposures of MMF; therefore, dose adjustment is not needed. Exposures to the inactive metabolite HES increased in parallel to the severity of renal impairment; however, the safety profile was comparable between subjects with renal impairment and HV. This is supported by summary presentation of (non-)clinical data demonstrating that HES metabolite is biologically inactive and pharmacologically inert. In study A105, no further biotransformation of HES in plasma or urine was reported. Moreover, no clinically meaningful findings in renal parameters have been observed in any of ten Phase 1 studies.

In Study A301, 845 subjects had normal eGFR (⩾ 90 mL/min/1.73 m2) and 205 subjects had mild decrease in eGFR (⩾ 60 to 90 mL/min/1.73 m2) at baseline. Evaluation of the safety profile for DRF in

subjects with normal eGFR and eGFR indicative of mild renal impairment does not suggest clinically significant differences. However, patients were excluded from the Phase 3 studies if they had an eGFR ⩽ 60 mL/min/1.73 m2 at screening (concerning seven subjects in Study A301). Moreover, study treatment was discontinued following an eGFR of < 60 mL/min/1.73m2 (persisting for more than four weeks after previous interruption of treatment). Therefore, no data is available on DRF safety in subjects with moderate and/or severe renal impairment, which is a missing information in the RMP.

A *post hoc* analysis was also performed on the safety population in 109MS303 (n=1736) to assess the incidence of TEAEs and SAEs in subjects with normal GFR (GFR ⩾ 90 mL/min/1.73 m2), mild renal impairment (GFR < 90 to ⩾ 60 mL/min/1.73 m2), or moderate to severe renal impairment (GFR < 60 mL/min/1.73 m2) at baseline. The proportion of patients with a TEAE or SAE during Study 109MS303 was similar in subjects with a normal GFR and in patients with mild renal impairment at baseline as was the most common TEAEs and SAEs. The most common (⩾ 15% in either GFR group) TEAEs by PT were MS relapse, nasopharyngitis, urinary tract infection, flushing, upper respiratory tract infection, headache, back pain, and diarrhoea. The most common (⩾ 5% in either group) treatment-emergent SAE by PT was MS relapse in both groups (normal GFR: 205 subjects [15%]; renal impairment: 34 subjects [8%]). The overall number of subjects in the *post hoc* defined group of "moderate to severe renal impairment" as per baseline status was low (n= 6 subjects). Therefore, interpretation of TEAEs and SAEs in this group needs to be treated with caution.

DRF has not been administered to MS patients with comorbid liver impairment. Thus, the safety profile in patients with hepatic impairment is an area of missing information in the RMP.

Patients were excluded from Phase 3 studies if they had ALT or AST values ⩾ 2x ULN at screening. Moreover, patients who experienced liver enzyme increases with DRF had to discontinue treatment if ALT or AST values remained > 3x ULN for ≥ 4 weeks (≥ 2 weeks for Study A302). The metabolism of DRF (like DMF) does not involve the CYP isoenzyme system; therefore, PK interactions with concomitantly administered drugs and subsequent increases in exposure of MMF are not expected. Available and missing data in patients with hepatic impairment is reflected in Sections 4.2, 4.4, and 5.2 of the SmPC for DRF in line with DMF.

Evaluation of intrinsic factors overall complied with information reported in the Tecfidera clinical programme.

No new concerns derive from evaluation of region as extrinsic factors with DRF and no such effect was observed in the Tecfidera clinical programme based on Pool A data. Some variability in the reporting of TEAEs/ SAEs/ TEAEs leading to discontinuation as well as TEAEs by SOC and preferred terms was observed for US versus non-US region, indicative of slightly increased incidences in the US population. This observation is not considered clinically relevant given that medical practice and therapeutic approaches as well as cultural/ socioeconomic factors are considered to differ. Moreover, in Study A302, safety results for DRF and DMF behaved similar with regard to region.

Neither DRF nor DMF have been studied in pregnant or lactating women.

Ten pregnancies were reported in the DRF studies, one in the Phase 1 Study A110 and nine pregnancies in Study A301 as of the interim data cut of 01 September 2020. DRF was discontinued as per the protocol. The outcome was known for eight of the ten pregnancies, including four full-term healthy infants, two elective abortions (at eight and ten weeks of gestation), and two spontaneous abortions. Two pregnancies were ongoing at the time of the data cut. The impact of DRF on pregnancy outcomes is proposed to be evaluated in a prospective pregnancy registry cohort study (Study 272MS401) for which the applicant confirmed that a study protocol will be submitted in a stand-alone procedure (MEA) following finalisation of the RMP and approval of the marketing authorisation.

At the time of the MA of Tecfidera, foetal abnormalities were not observed in 38 human pregnancies

reported in subjects exposed to DMF. Animal studies have shown reproductive toxicity and Tecfidera is not recommended during pregnancy and in women of childbearing potential not using appropriate contraception. In Study 109MS303, 34 pregnancies were reported as per the data cut-off 08 November 2019, including a single pregnancy in the partner of a male patient treated with Tecfidera. 68% of all reported pregnancies resulted in live births. 4 cases of spontaneous abortion/ undeveloped pregnancy (12%) occurred at ≤ 15 weeks gestation and two pregnancies resulted in elective terminations. The outcome of the two pregnancies was unknown (lost to follow-up). For three cases (9%) of induced abortion due to congenital abnormalities, the narratives were insufficient to rule out a causality with Tecfidera treatment, i.e., one case of reduction deformity of the left upper limb lacking any genetic predisposition (rated as possibly related to Tecfidera) in a young patient; one case of triploidy (rated as unlikely related to Tecfidera); one case of trisomy 21 and cardiac failure reported in the foetus (rated as not related to Tecfidera). The three cases of congenital abnormalities exceeded the background prevalence rate of a reference population in EUROCAT. So far, no immediate action or changes to the product information has been anticipated based on these cases and further information is expected from a cumulative analysis on pregnancies in the upcoming PSUR (submission date 24 June 2021, under evaluation in EMEA/H/C/PSUSA/00010143/202103 at the time of this assessment).

The safety of DRF in paediatric patients has not been established so far. An application for a PIP, including a request for deferral and a waiver for patients aged 0 to 10 years, was submitted to EMA on 17 December 2019 and has been agreed upon (EMEA-002685-PIP02-19).

For DMF, two paediatric studies in patients aged 13 to < 18 years have been conducted, i.e., a 24-week, open-label, prospective, uncontrolled study in 22 paediatric subjects with RRMS (109MS202; reference is made to EMEA/H/C/002601/II/0042) and its 96-week extension (109MS311; reference is made to EMEA/H/C/002601/II/0059). These studies were not part of the PIP for DMF. Based on the limited number of paediatric subjects treated with DMF in these two studies, clinical safety appears in line with the adult profile. Information deriving from these two small paediatric studies with DMF is not considered of clinical relevance for DRF; as such, references have been agreed to be deleted in the product information for DRF. An OL, randomised, multicentre, multiple-dose, active-controlled, parallel group, efficacy and safety study of BG00012 in children from 10 to less than 18 years of age with RRMS (109MS306), agreed on in the PIP for Tecfidera (P/0177/2020), has meanwhile been finalised and results of this study are assessed in a parallel procedure (EMEA/H/C/002601/II/0073) to support treatment with DMF in paediatric patients.

Experience with overdose in MS patients treated with DRF in the Phase 3 studies is very limited. In Studies A301 and A302, one subject each was reported to have had a TEAE of overdose. Accidental overdose in the patient from Study A301 was reported as SAE. No cases of overdose have been reported in DMF clinical trials.

No evidence of abuse potential could be demonstrated based on the assessment of pre-defined MedDRA search criteria. The overall incidence of TEAEs related to abuse was 7.3% in Study A301, 5.4% of them with rather unspecific reports of dizziness. Dizziness was likewise reported as TEAE within the AESI category of cardiac disorders. No additional concern derives from adherence rates (>100%) evaluated in Studies A301 and A302.

2.6.8.7. Immunological events

Not applicable.

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

With regard to its biotransformation, no CYP interaction and protein binding is expected with DRF in line with DMF. *In vitro* studies demonstrated that MMF, DRF, HES, and RDC-8439 do not inhibit or induce CYP enzymes at clinically relevant concentrations. A Phase 1 DDI study with digoxin was conducted given that DRF showed potential to inhibit P-gp transport *in vitro*; however, no effect on P-gp transport *in vivo* could be deduced. No unexpected safety issues derived from digoxin administration.

According to the biotransformation of DMF (hydrolysis to MMF and further transformation through the TCA cycle, with exhalation of CO2 as a major elimination route and secondary renal elimination) the interaction potential seems to be low, especially with respect to CYP interaction and protein binding. No systematic DDI study was conducted.

In Study 109HV106, no new safety signals were detected in 56 healthy volunteers who received repeated doses of either DMF (total daily doses ranging from 480 to 720 mg) or placebo with or without ASA for four days.

In Study 109HV113, the safety profile of concurrent use of Ortho Cyclen (an oral contraceptive with norelgestromin and ethinyl oestradiol) and DMF was consistent with that observed for DMF. The coadministration of DMF with this combined oral contraceptive did not elicit any relevant effects in oral contraceptive exposure. Reference is made to EMEA/H/C/002601/II/0037 and results are depicted in Section 4.5 of the SmPC. No interaction studies have been performed with oral contraceptives containing other progestogens.

The MMF pharmacokinetics (DMF 240mg TID for 3 and 2 days, respectively) were not altered in the presence of Avonex and GA.

Concomitant administration of acetylsalicylic acid (Aspirin) and vaccination was studied with Tecfidera in healthy volunteers or MS patients and is therefore likewise relevant for DRF:

No safety concerns derived from HV/ MS patients treated with Aspirin in addition to DMF treatment based on additional Studies 109HV321 and 109MS406 (reference is made to EMEA/H/C/002601/II/0036G). The effect on concomitant ASA administration on related flushing events in these subjects is described in the DMF and DRF product information (SmPC sections 4.4 and/ or 4.5).

No additional safety concern derived from vaccination of MS patients with non-live vaccines (with either a recall antigen (Td), T-cell independent antigen (PPSV23), or a neoantigen (MCV4)) in addition to Tecfidera treatment (reference is made to EMEA/H/C/002601/II/0028). The results and recommendations deriving from this study is reflected in the DMF product information (SmPC section 4.5), and in the DRF product information.

2.6.8.9. Discontinuation due to adverse events

Five subjects discontinued from any Phase 1 study due to TEAEs, which were rated as related to treatment in three patients (hypersensitivity, blood CK increased, and papular rash).

In the Phase 3 DRF studies, subjects who discontinued due to TEAEs were at the same time withdrawn from the study.

The incidence of discontinuations due to TEAEs was 8% for subjects in Study A301. TEAEs leading to discontinuation of DRF in > 1 subject per treatment group were as follows: lymphopenia (1.3%, 14 subjects), MS relapse (1%, 11 subjects), lymphocyte count decreased (0.7%, 7 subjects), flushing (5 subjects), diarrhoea and ALT increased (3 subjects each), and 2 subjects each for glomerular filtration

rate decreased, LFT increased, and urticaria. 2 subjects discontinued treatment due to hypersensitivity TEAEs in the de novo group.

Of 3.8% discontinuations due to AEs in Study A302, 1.6% occurred on DRF and 6% on DMF. Of these, 0.8% of subjects on DRF and 4.8% of subjects on DMF discontinued the study due to GI AEs. The majority of these events were of mild and moderate severity, assessed as related to treatment and resolved by the end of the study; the 3 severe GI events leading to discontinuation occurred in the DMF treatment group. Other TEAEs leading to discontinuation in one patient each were suicide attempt, dermatitis allergic (both in the DRF group), depression, and urticaria (both in the DMF group).

AEs leading to dose reduction or dose interruption (only allowed in A301) were reported in 8% of patients in Study A301, a majority of them belonging to the *de novo* group. TEAEs leading to dose reduction or dose interruption in ≥ two subjects were lymphopenia/ lymphocyte count decreased (n=17 and n=11), diarrhoea (n=5), nausea (n=3), flushing (n=6), and two subjects each for abdominal pain, chronic gastritis, ALT increased, AST increased, erythema, pruritus, urticaria, leukopenia, pain in extremity, dyspnoea, vomiting, vision blurred, and dizziness.

Discontinuations from study treatment and withdrawal from study due to AEs in the DMF Pool A were more frequent in the DMF groups compared to placebo (14% DMF and 11% placebo), and headed by MS relapse (6% placebo vs. 1% DMF 240mg BID, and 2% DMF 240mg TID). AEs leading to treatment discontinuation with higher incidences in DMF-treated subjects compared to placebo and GA were reported for GI disorders, flushing, and skin and subcutaneous disorders SOCs (less than 1% in the placebo and GA groups and in up to 6% of patients in the DMF groups). The pattern of AEs leading to withdrawal from study was similar to that observed for AEs leading to discontinuation of study treatment. Data from Studies 109MS301 and 109MS302 indicated a higher discontinuation rate for subjects on DMF compared to placebo for the first year (especially the first three months) of treatment, likely associated with the occurrence of flushing and GI events. GI events and flushing events were also the main reason for dose reductions and interruptions in the DMF studies.

Long-term treatment with DMF in Study 109MS303 led to discontinuations from treatment due to an AE in 16% of subjects, mainly due to MS relapse and lymphopenia, and lymphocyte count decreased.

2.6.8.10. Post marketing experience

No new safety signals have been confirmed based on DRF post-marketing data following its approval in the US in 2019.

However, a number of safety signals came up for DMF after approval of Tecfidera on 30 January 2014.

The safety signal for PML arose early after approval of Tecfidera following the first confirmed case of PML (a fatal event) in a patient with severe prolonged lymphopenia (> 3.5 years) in a clinical study. The risk for PML has been taken up in regulatory procedures either from a mechanistical perspective (lymphocytopenia) or based on additional confirmed cases. Reference is made to EMEA/H/C/WS0689/G, EMEA/H/C/002601/II/0026, EMEA/H/C/002601/II/0030, EMEA/H/C/002601/R/0053, EMEA/H/C/002601/II/0030, EMEA/H/C/2601/II/54/G, EMEA/H/C/2601/II/58, and EMEA/H/C/2601/II/63). So far, 12 PML cases have been confirmed for Tecfidera, which all occurred in patients with ALC below LLN (<0.91x109/L), and 11 of these cases occurred post marketing. Substantial amendments have been introduced in the product information of Tecfidera, including a contraindication in patients with suspected or confirmed PML, detailed warnings (stopping rules, additional factors that might increase the risk for PML and demand increased vigilance), and description of study findings for lymphocyte subsets in Section 4.8. Based on MMF being the same active moiety of DMF and DRF, the same risk applies to DRF.

At present, lymphopenia seems to increase the risk for PML. Therefore, the mechanism of decreases in lymphocyte counts has been evaluated in nonclinical and clinical studies. While nonclinical investigations ruled out selective toxicity of DMF and MMF on human lymphocytes during Tecfidera treatment, a mechanistic rational for the effect of DMF on lymphocytes could not be deduced from clinical studies. However, quantitative and qualitative changes within the lymphocyte subpopulations (specifically CD4+ and CD8+ T cells) in DMF-treated patients have been observed in Study 109MS310, for which results are included in Section 4.8 of the Tecfidera SmPC. Given the role of CD4+ and CD8+ T cells in the immunological defence against opportunistic infections, it is mechanistically plausible that loss of these subsets enhances the susceptibility for PML. In particular, the decline of CD8+ T cells has recently been related to the pharmacological activity of DMF.

The weighted cumulative evidence that derived from a review of post marketing data in line with clinically significant cases of reversible liver injury (Drug-induced liver injury), including liver enzyme increases (≥ 3x ULN) and elevation of total bilirubin levels (≥ 2x ULN) was deemed sufficient to support a causal association between hepatotoxicity and DMF. Consequently, hepatic injury, which was initially categorised as an important potential risk, was re-categorised as an important identified risk (drug-induced liver injury) for DMF in the RMP. None of the reported cases resulted in liver failure, liver transplantation, or death. Cumulatively, for DMF (up to 26 March 2020), a total of 770 events of progressive hepatic injury in 748 cases were received, of which 267 were HCP-confirmed events and 503 were consumer-reported events. A warning on hepatic findings and monitoring requirements as well as respective ADRs have been included in Sections 4.4 and 4.8 of the Tecfidera/ DRF SmPC. DILI is included as an important identified risk in the Tecfidera and DRF RMP.

Safety signals of overdose, anaphylaxis and thrombocytopenia were reported in the postmarketing experience and relevant information has been included in the Tecfidera/ DRF product information.

A safety signal of Herpes zoster derived from cumulative clinical and postmarketing evidence for Tecfidera and adequate warning and description of this ADR and its presentation has been added in the product information to also include that in a majority of patients concurrent lymphocyte counts met the criteria of moderate to severe lymphopenia.

Recently, cases of Fanconi syndrome have been reported for a DMF-containing product in combination with other fumaric acid esters, while no such case derived from treatment with Tecfidera. Given that MMF is the active moiety in both drug products, this warning was deemed adequate for Tecfidera and is likewise proposed for DRF.

2.6.9. Discussion on clinical safety

The applicant developed a gastro-resistant drug product, which contains a core of DRF minitablets (231 mg per capsule). The amount of DRF in two capsules (i.e. 462 mg DRF) is bioequivalent to 240 mg DMF contained in Tecfidera, which is an established treatment for adult patients with RRMS in Europe since 2014. Given that DRF and DMF are different prodrugs sharing the same active moiety MMF, relying on the safety profile of DMF is considered acceptable for the present application. No pivotal clinical studies have been conducted with DRF; therefore, the pivotal Phase 2 and 3 studies for DMF in Tecfidera serve as key information for the safety of DRF.

Product-specific evaluation of clinical safety derives from two clinical phase 3 studies with DRF, i.e., from Study A302, an active - controlled study with DMF and a treatment period of 5 weeks (including a 1 week titration period), and from Study A301, an ongoing OL study of 96 weeks of DRF treatment, which enrolled subjects from Study A302 and also de novo subjects.

The integrated safety database for Tecfidera refers to four clinical studies in adult subjects with RRMS (partly placebo-controlled Phase 2 study C-1900; placebo-controlled Phase 3 studies 109MS301 and 109MS302; and open-label extension 109MS303). Pooling of Phase 2 and Phase 3 DMF clinical studies for assessing safety focusses on the placebo-controlled experience with Tecfidera (Pool A) and on the DMF experience from controlled and uncontrolled safety data (Pool B, including preliminary data in study 109MS303 for up to 5 years; cut-off date 3 August 2011). Moreover, it is cross-referred to an ongoing variation procedure EMEA/H/C/002601/II/0069/G, in which the final CSR from 109MS303 is under evaluation at the time of this assessment. This study comprises a treatment period of at least eight years in addition to treatment with DMF in the parent Studies 301 and 302. Any outcome of this variation relevant to the product information for Tecfidera has been confirmed by the applicant to be reflected in the DRF PI.

Patient exposure

The majority of subjects treated with either DRF or DMF in Study A302 (i.e. ~95% and 90%), rolled over to receive open-label DRF in Study A301. In addition, 593 patients who had not participated in any prior DRF study received DRF as *de novo* subjects. Mean (SD) exposure to DRF in any of the two Phase 3 studies was 523.9 days (213.61) in 1071 subjects with at least one dose of DRF per the original data cut-off 7 February 2020 and a total of 1536.21 subject -years of exposure. Contribution of Study A302 to the overall subject exposure to DRF is negligible with a mean (SD) exposure of 35.2 (4.16) days. Therefore, Study A302 adds to the understanding of short-term DRF and DMF safety and tolerability issues, i.e., GI disorders, flushing and related events, and elevations of liver enzymes. In contrast, immunomodulating effects like infections and malignancies need longer treatment durations to develop and can at best be retrieved from A301, although, lacking an active comparison. As per the data cut-off 01 September 2020, completed data are available from 659 of 1057 (62.3%) subjects in A301. 152 of 1057 subjects (14.4%) are still ongoing in A301. Updated safety data do not pose additional safety concerns. In both DRF studies combined (original data cut-off 7 February 2020), 972 subjects (88.6%) have received DRF for more than six months. 826 subjects (75.3%) and 499 patients (45.5%) received DRF for more than 12 months and 24 months, respectively. Moreover, supportive (short-term and variable) exposure derives from Phase 1 studies conducted in healthy volunteers and subjects with renal impairment (n= 390 in total). 139 (13.2%) of subjects in A301 were > 55 years of age (inclusion criteria allowed patients to be included in A301 up to the age of 65 years), with three subjects aged 65 years at Baseline. Thus, the "safety profile in patients older than 65 years" is a missing information in the RMP (contrasting Tecfidera, for which the age cut-off is 55 years).

The vast majority of safety data relies on Tecfidera (EPAR reference EMEA/H/C/002601/0000/Rev 1). Controlled safety data (Pool A) is available for 1720 DMF-treated subjects and 836 placebo-treated subjects, summing up to 2323.5 subject-years of DMF exposure. Overall, 2468 subjects were exposed to DMF in Pool B and of these, 1429 (1056) were exposed for ≥1 year (≥2 years) at doses ≥240 mg DMF BID. Moreover, Study 109MS303 with data cut-off as per 8 November 2019 adds to the DMF safety data a median (min, max) of 5.848 years (0.00, 9.43) on DMF relating to 1736 subjects, representing 8896.19 subject-years of exposure.

Adverse events (and related laboratory findings)

(Very) common adverse events associated with DMF treatment are GI disorders (including diarrhoea, nausea, abdominal pain upper, abdominal pain and vomiting), flushing, skin and subcutaneous disorders (pruritus, rash, erythema), haematological abnormalities (lymphopenia and leukopenia), increased hepatic enzymes, and proteinuria.

AEs reported with DRF in Studies A301 and A302, their frequency, severity, relation to treatment, and the time to onset were found to be aligned with the expectations with Tecfidera. No product-specific concerns have been identified. Therefore, it is assumed that safety data from the Tecfidera clinical studies

form the basis of the DRF product information and to add or adjust with DRF data if these are considered sufficiently robust to supersede specific Tecfidera information. Upon request, adverse events with DRF in the product information have been based on the concept of *treatment-emergence* in line with Tecfidera.

In Study A301, 88.2% of subjects reported at least 1 TEAE. In Study A302, a similar proportion of subjects reported at least 1 TEAE in the DRF group (78.3%) and in the DMF group (83.7%). TEAEs were considered *treatment-related* in a majority of these subjects. Most of the TEAEs in both studies were mild or moderate in severity, with < 10% of TEAEs rated as severe.

In Study A301, the most common TEAEs were flushing (27.2%), MS relapse (19%), URTI (14.3%), nasopharyngitis (12.9%), lymphopenia (11.2 %), and diarrhoea (10.3%). The pattern and frequency of TEAEs is compatible with a longer treatment duration in this study. Moreover, in Study A301, events with an onset early after treatment initiation were numerically higher in de novo subjects as compared to rollover subjects from either DRF DMF in A302.

In Study A302, common TEAEs were comparable for DRF and DMF. The most frequently reported TEAEs were those known to occur early during treatment (onset within the first month of treatment), i.e., flushing and flushing-related events (50.4% overall [RF: 45.8%, DMF: 55%]) and GI events (41.9% overall; diarrhoea 18.8% overall [DRF: 15.4%, DMF: 22.3%], nausea 17.7% overall [DRF: 14.6%, DMF: 20.7%]).

Flushing and flushing-related events in both DRF studies were in line with incidences in the Tecfidera safety pools (42% and 41% in Pool A and B, respectively, for DMF 240 mg BID), and also regarding severity and time interval of reporting (during the first three months).

Gastrointestinal disorder TEAEs are among the most frequently reported side effects of DMF-containing drug products, with incidences between 33% (in study 109MS303) and 48% (in Pool A) for DMF 240 mg BID and in line with data deriving from the psoriasis indication (reference is made to the EPAR of Skilarence EMEA/H/C/002157/0000). The incidence of GI events, mainly diarrhoea, nausea, and abdominal pain, with DRF appears to be similar: in A301, reporting was highest during the first three months of treatment and more frequently in *de novo* subjects. Overall, 31.6% reported GI disorders TEAEs, and 0.9% of subjects reported serious GI disorders. 1.8% of subjects had a dose reduction/ interruption due to GI events. In Study A302, the overall incidence in both groups combined was 41.9%, with a lower reporting in the DRF group as compared to the DMF group (34.8% vs. 49%). Gastrointestinal tolerability has been designated as AESI, for which only SAEs and AEs leading to discontinuation were taken into account. GI AESIs in A302 were reported more frequently in the DMF group vs. the DRF group (4.8% vs. 0.8%), all of them leading to discontinuation. The two events in the DRF group were diarrhoea and vomiting, while abdominal pain upper was the leading GI event in the DMF group.

The clinical relevance of a slightly lower reporting of the most common GI TEAEs (i.e., diarrhoea, nausea, abdominal pain upper, abdominal pain, and vomiting) and discontinuations due to GI events as well as GI AESI in the DRF versus the DMF group in A302 is, however, debatable given that:

- the difference is based on a 5-week treatment duration in A302 (including a 1-week titration to the full dose),

- GI events do not appear different for DRF and DMF based on longer treatment durations in Study A301 (DRF: 31.6%) and in 109MS303 (DMF: ~30% up to the data cut-off 03 August 2011 and 35% up to the data cut-off 08 November 2019). Moreover, and as indicated for evaluation of the primary endpoint in Study A302, there are several shortcomings, including the lack of validated scales for investigation of GI tolerability, the choice of Number of Days with any IGISIS Symptom Intensity Score ≥ 2 as an appropriate endpoint, the robustness of the statistical analyses, and the lack of concordance between

the "efficacy" findings for better GI tolerability and the reported GI TEAEs in a number of treated days (10 to 11%). Thus, the informative value of the study claiming favourable GI tolerability has found to be low and the clinical relevance of numerical differences in GI tolerability between DRF and DMF could not be deduced from the provided data.

The proposed mechanism behind the claimed increase in GI tolerability of DRF compared with DMF is considered hypothetical, with reasons mentioned by the applicant being the lower concentration of methanol formed, the larger particle size of DRF limiting binding to receptors within the gastrointestinal tract, and the lower electrophilicity of DRF.

Events captured as GI AESI in A301 (reported in 0.8% of subjects) were qualitatively in line with the reference product Tecfidera, including abdominal pain, diarrhoea, gastritis and vomiting. However, direct comparison to the DMF/ Tecfidera clinical experience is misleading given that the definition of AESI in the DRF and DMF programme was different. The Tecfidera SmPC Section 4.8 indicates an onset within the first month of treatment while events may continue to occur intermittently throughout treatment, which is likewise applicable to DRF.

In Study A302, patients were instructed to "take study drug with or without food". The intake with food is anticipated to improve tolerability of DMF and likewise of DRF in subjects experiencing flushing or GI adverse reactions, which has been added to Section 4.2 of the DRF SmPC.

Product-specific ADRs for DRF in Table 1 in Section 4.8 of the SmPC have been justified by the applicant to be dispensable given that the design of the Phase 3 DRF studies does not allow to derive ADRs (no placebo control and OL) and no increased incidence in TEAEs has been observed in these studies. Therefore, it is acceptable to rely on the ADRs for Tecfidera.

Adverse events of special interest in line with the known safety profile of DMF deriving from clinical studies and post marketing experience were assessed for DRF, including anaphylaxis/ angioedema, opportunistic infections, all serious infections, lymphopenia, liver injury, malignancies and premalignant conditions, renal injury, cardiac disorders, pancreatitis, and GI tolerability.

Anaphylaxis and angioedema as well as events of pancreatitis were neither reported in Study A302 nor in Study A301.

Almost half of the subjects in A301 had TEAEs from the infections and infestations SOC in line with Tecfidera. *Serious and opportunistic infections* (other than PML and herpes zoster) constitute an important potential risk in the RMPs of DMF and DRF. No such events were reported during A302. In A301, 0.6% of subjects had non-systemic, mild to moderate candida infections. Mild to moderate herpes zoster/ varicella zoster virus infections occurred in ~2% of subjects.

Eleven PML cases have been confirmed in patients treated with Tecfidera after marketing authorisation in 2014 in addition to a single subject with fatal outcome in clinical Study 109MS303. Lymphopenia is a risk factor for serious and/or opportunistic infections, including PML, in patients treated with fumarates (reference is also made to the EPAR of Skilarence EMEA/H/C/002157/0000). Lymphopenia with lymphocyte counts below LLN ($<0.91x10^9$/L) was a commonality in all PML cases. Substantial amendments on lymphopenia and PML have recently been implemented in the product information for Tecfidera following variation EMEA/H/C/2601/II/63, also including a contraindication in patients with suspected or confirmed PML. Given its rarity, it is not unexpected that PML has not been reported with DRF so far.

0.9% of subjects in A301 had *serious infections*, amongst them one subject with a fatal TEAE of pneumonia (bacterial). Although, this event was not rated related to DRF, a contribution cannot be excluded. While a relation between serious infections and minimum post-baseline lymphocyte counts could not be established for DMF based on pivotal Phase 3 study data, the lack of a relation between

serious infections and severe prolonged lymphopenia cannot be assessed for DRF given that ALC < $0.5x10^9$/L persisting for > 4 weeks led to discontinuation from treatment in DRF studies.

Lymphopenia (incl. lymphocyte count decreased) is an expected side effect of DMF and DRF treatment, with decreases in leukocyte and lymphocyte counts being an identified risk in the RMPs. Decreases in lymphocyte (and leukocyte) counts starting at Week 4 through Week 48 with a plateau up to Week 96 were noted for DRF in line with Tecfidera. Mean decreases were identical to those observed in DMF clinical studies, i.e., 30% and 11% for lymphocyte and leukocyte counts, respectively. As per the data cut-off, 42.4% of subjects in A301 (443 of 1045 with available ALC) had lymphocyte counts below LLN (< 0.91×10^9/L) with lymphopenia being reported as moderate (CTCAE Grade 2) in a majority of these subjects (236 of 443). In 13.7% of all subjects (143 of 1045), moderate lymphopenia was prolonged for six months and longer and the incidence was slightly higher in DRF *de novo* subjects and DRF rollovers from A302 as compared to DMF rollovers from A302, probably owing to the fact that treatment duration in patients from the DMF group was shorter.

While severe lymphopenia (ALC < 0.5×10^9/L) was reported in 8.9% (93 of 1045) of subjects, in none of these subjects the lymphopenia was prolonged for more than six months given that subjects with lymphocyte counts < 0.5×10^9/L for ≥ 4 weeks were to be discontinued from treatment. Information on post-discontinuation lymphocyte recovery is clinically important to judge the risk for (serious) infections and to decide on treatment initiation with other DMTs. A 6-months interval of post-discontinuation monitoring for subjects in A301 with ALC < $0.8x10^9$/L at the end of treatment showed that recovery of ALC to ≥LLN was not achieved in all patients. In DMF long-term Study 109MS303, ALC in more than half of subjects with ALC < LLN at recovery baseline and < $0.8x10^9$/L at recovery baseline recovered to ≥ LLN within the follow-up period (up to 48 weeks). However, a number of uncertainties have been identified for the datasets and statistical analysis underlying this evaluation in variation EMEA/H/C/002601/II/0069/G (under evaluation at the time of this assessment), which, at present, precludes ALC recovery data to be included in Sections 4.8 and 5.1 of the SmPCs for Tecfidera and Vumerity. Agreement from the applicant has been received. TEAEs of lymphopenia/ lymphocyte count decreased have been reported in 16.7% of patients in Study A301, with slightly more subjects from the rollover DMF and DRF groups. Incidences were similar in the first and second year of treatment and in less than half of these events, lymphopenia did not resolve by the data cut-off. TEAEs of lymphopenia and lymphocyte count decreased combined was the main reason for dose reduction/ interruption in A301 (2.6% of patients). Owing to the short treatment duration in A302, lymphopenia was reported as TEAE in 0.8% of all patients only.

For DMF and DRF, monitoring of complete blood counts, including lymphocytes needs to be performed prior to treatment initiation and every three months. Discontinuation of treatment in subjects with prolonged severe lymphopenia (lymphocyte counts <$0.5x10^9$/L) persisting for more than six months is recommended as well as re-assessment of the benefit/risk in subjects with sustained moderate reductions of absolute lymphocyte counts ≥$0.5x\ 10^9$/L and < $0.8x\ 10^9$/L for more than six months. In patients with ALC<LLN, regular monitoring of lymphocytes is advised, and additional factors might further augment the individual PML risk.

No new signal derives from the DRF clinical programme regarding the nature and the incidence of *malignancies*, which is also not expected given the duration of the studies. Malignancies were reported in 0.5% in A301, including basal cell carcinoma, squamous cell carcinoma, diffuse large B-cell lymphoma, invasive ductal breast carcinoma, and malignant melanoma. In 0.7% of subjects, pre-malignant conditions were recorded. In the Tecfidera clinical programme, malignancies reported in the DMF groups were low and similar to placebo and GA (≤ 1%; transitional cell carcinoma of renal pelvis, basal cell skin carcinoma, breast cancer and cervix cancer in the DMF groups). Long-term treatment with DMF of at least eight years in Study 109MS303 was not found to increase the risk for malignancies, but results

from PASS Study 109MS401 is expected to further inform on this potential risk. Moreover, additional analyses on malignancies and background rates with focus on skin cancers have been requested in the ongoing variation EMEA/H/C/002601/II/0069/G to be presented in the upcoming PSUR (PSUR submission date 24 June 2021, under evaluation in EMEA/H/C/PSUSA/00010143/202103 at the time of this assessment). These data might entail amendments to the product information of Tecfidera and DRF. Malignancies are also a potential risk with DRF in the RMP in line with DMF (in Tecfidera).

Transient mean increases in liver transaminases with DMF typically develop within the first 4 weeks of treatment. In a majority of subjects, elevation in ALT and/ or AST remain below 3x ULN. The incidence of TEAE associated with liver injury in A301 was 7.2% overall, with 5.5% and 2.9% of events being increased liver transaminases ALT and AST, most frequently reported within the first 2 months of treatment. ALT and AST values > 3x ULN were reported in 2% and 1.1% of subjects, in line with results for hepatic events in the DMF clinical pools. Less than 1% of subjects experienced ALT or AST of >5x ULN, >10x ULN, or increases in total bilirubin of >1.5x ULN, and the incidence was even lower in A302. No subject fulfilled criteria of Hy's law in the DRF and DMF clinical programme. Cholestatic liver injury, hepatic steatosis, and hepatosplenomegaly were each reported in a single subject in A301. Few events were serious or led to treatment discontinuation. Drug-induced *liver injury* is an identified risk for DMF and likewise DRF. Monitoring of liver enzymes is recommended in the product information. A signal of *renal toxicity* derived from nonclinical studies with DMF. However, DMF was not found to be associated with an increased risk of renal or urinary events, neither in pivotal studies nor in the long-term extension study (109MS303). Proteinuria, haematuria, and microalbuminuria were each reported in less than 10% of patients. These events were mild to moderate in severity and rarely led to treatment discontinuations. In DRF studies A301 and A302, events including their incidences were essentially in accordance with those for Tecfidera, e.g., proteinuria was reported as TEAE in 1.3% of patients in A301. There was no evidence for impaired renal function with DRF treatment in studies A301 and A302 based on mean serum parameters of albumin, creatinine, urate, BUN, or GFR over time, shift analyses, and potentially clinically significant abnormalities. Urinalysis results were found in line with Tecfidera, i.e. urine protein, urine ketones and urine occult blood in 76.6%, 55.3%, and 37.4% of patients in A301; however, as with Tecfidera, results did not correlate with renal injury TEAEs. Proteinuria and ketonuria are labelled for Tecfidera and also for DRF. A PCS of abnormal β2-microglobulin (defined as > 0.300 mg/L) was reported in 15.3% of subjects in A301; however, no significant changes in β2-microglobulin and microalbumin indicative of renal tubular damage were noted across DMF treatment groups up to 12 years of treatment in 109MS303.

No increased risk on *cardiac* safety could be deduced from DRF treatment and did not emerge during human therapy with DMF. However, patients with significant cardiovascular conditions were excluded from clinical trials. Phase 1 studies with DRF revealed ventricular extrasystoles as main finding. In addition, single subjects reported presyncope, palpitations, chest discomfort, dyspnoea, tachycardia and sinus tachycardia. In study A301, almost half of the subjects reported with cardiac disorders – related TEAEs had rather unspecific dizziness (5.4%). All other TEAEs were reported in ≤ 1.5% of subjects. Two cardiac-related severe SAEs, hypertensive heart disease (in a patient with contributing medical conditions) and cardiac arrest, were fatal. Vital signs and ECG results in Studies A301 and A302 were unremarkable.

Four *deaths* were reported with DRF, all of which occurred during Study A301 and considered not related to DRF by the Investigator. Reasons for death were pneumonia bacterial with subsequent acute respiratory failure, fall (intention unspecified), hypertensive heart disease (in a subject with relevant medical history and pre-existing condition, e.g., hypercholesterolaemia), and sudden cardiac arrest. While a contribution of DRF to these deaths cannot be ruled out, none of these death cases poses an additional concern over DMF/ Tecfidera – reported deaths in the respective clinical programme.

No additional concern derives from the reporting of *serious adverse events* in the DRF studies: The overall incidence of SAEs in A301 was 11.4% (n= 120 subjects), with MS relapse accounting for half of the SAEs, which is consistent with reporting of SAEs in the Tecfidera safety pools with MS relapse being the most frequently reported SAE. Infections and GI disorders were serious in few subjects only (0.7% and 0.9%). SAEs were rated as treatment-related in 0.9% (n=10) subjects, with almost half of them from the GI disorders SOC. In Study A302, a similar number of subjects in both groups reported SAEs (1.4% in total [7 subjects]), which were assessed as not related to study treatment and were recovered/resolved or resolved with sequelae by the end of the study. MS relapse was the only SAE reported in more than 1 patient in each group.

Discontinuations due to TEAEs were low in study A302 (3.8% of all patients; 1.6% in the DRF group and 6% in the DMF group) with GI tolerability AEs being the reason in half of the discontinued subjects on DRF and in all but two subjects on DMF. Discontinuations in A301 (8% of patients) were mainly due to events known to occur with longer treatment duration, i.e., MS relapse and lymphopenia/ lymphocyte count decreased. Discontinuations due to lymphopenia were not reported in the DMF pivotal trials given that low lymphocyte counts were not a stopping criterion. Lymphopenia as a reason for discontinuation of DMF was first reported in 109MS303 (in 1% of DMF subjects). As expected, discontinuations due to GI events were lower in A301 as in A302 and more frequent in the *de novo* group.

No significant findings were retrieved for haematology, chemistry, and urinalysis *laboratory parameters* not mentioned in previous sections, except for a transient increase in eosinophils during the first 2 months of treatment, which is labelled for DMF and was likewise observed in A302 and in the de novo DRF group in Study A301.

There were no relevant changes or findings in *vital sign* parameters, QTc interval or any other quantitative or qualitative ECG parameter changes. Any potentially clinically significant values observed for DRF were in line with the DMF clinical study experience.

Data from the DRF clinical programme do not indicate an increased risk for *suicidality* with DRF treatment and no such risk has been identified with DMF. Based on the C-SSRS, which was not routinely conducted in the DMF clinical programme, an increase of suicidal ideation post-baseline over baseline was reported in all subjects (2.1% vs. 0.2%). However, this is not unexpected in a population with an increased prevalence of depression over a longer period.

DRF (like DMF) was not found to bear a risk for *abuse potential*.

Safety in special populations

Similar to DMF, the safety profile of DRF in MS patients seems comparable across gender, age and other intrinsic and extrinsic factors based on the data presented and with some variability in reporting of adverse events. However, this is not considered of clinical relevance. The safety profile of DRF in subjects ≥ 55 years of age seems comparable to the safety profile in subjects < 55 years of age based upon additional analysis of TEAEs provided by the applicant. This is relevant given that DMF clinical safety data are only available (and thus supportive for DRF) in subjects up to 55 years of age. The quality of available (uncontrolled) DRF data in the elderly up to an age of 65 years in now adequately reflected in Section 4.2 of the DRF SmPC.

No correlation between *renal impairment* severity and MMF exposure was observed in a Phase 1 study in subjects with no, mild, moderate, or severe renal impairment. However, no differences in the safety profile (based on reporting of TEAEs and SAEs) could be observed in this study. In support of these findings, no qualitative and quantitative difference in the safety profile was noted in patients with normal renal function and patients with mild renal impairment in A301. This is in line with the results from a post-hoc analysis in the DMF extension study 109MS303. No dose adjustment of DRF (like with DMF) is required based on these findings. DRF (and likewise DMF) has not been administered to patients with

(persisting) moderate and/ or severe renal impairment and this is considered a missing information in the RMP and labelled in Sections 4.2 and 5.2 of the SmPC. In addition, the applicant provided adequate (non-) clinical data demonstrating that HES metabolite is biologically inactive and pharmacologically inert. Although HES accumulation was shown with increasing renal impairment, the safety profile was comparable between subjects with renal impairment and those with normal renal function.

No studies with DRF were conducted in patients with *liver impairment*. DRF is metabolised by esterases and MMF is metabolised through the TCA cycle, without CYP isoenzyme involvement; thus, hepatic impairment is not assumed to alter PK of DRF or MMF and this is labelled in Sections 4.2 and 5.2 of the SmPC.

No safety signal of foetal abnormalities derives from ten pregnancies reported in the DRF clinical programme. No such abnormalities have been identified in the controlled clinical DMF programme. In line with Tecfidera, DRF is not recommended during *pregnancy* and in women of childbearing potential not using appropriate contraception given that animal studies have shown reproductive toxicity. The impact of DRF on pregnancy outcomes will be evaluated in a prospective pregnancy registry cohort study (Study 272MS401). In addition, a retrospective analysis of respective pregnancy data from European product-independent MS and pregnancy registries might be considered at a later time point (post-authorisation), once exposure data becomes available for Vumerity, facilitating a decision about suitable national registries across the EU. No additional information on pregnancy outcome with DMF on 3 cases of congenital abnormalities could be retrieved from study 109MS303 (in EMEA/H/C/002601/II/0069/G (under evaluation at the time of this assessment).

The safety of DRF has not been studied in *paediatric patients*. The PIP for DRF includes two clinical studies in patients 10 to less than 18 years of age with RRMS. Paediatric data available for DMF (based on two small studies not included in the PIP for Tecfidera) do not indicate an altered safety profile. However, given that available paediatric safety data for DMF are based on a small and uncontrolled dataset, this information is of limited value for DRF and has been agreed by the applicant to be deleted in the product information.

With regard to *drug-drug interactions*, *in vitro* studies demonstrated that neither DRF nor MMF (or metabolites) inhibit or induce CYP enzymes at clinically relevant concentrations. While DRF showed the potential to inhibit P-gp transport *in vitro* (but not to induce it), this could not be confirmed in a single *in vivo* DDI study with digoxin. Therefore, formal interaction studies were not conducted and DRF, like DMF, is not suspected to alter the PK of concomitantly administered drugs. Additional data are available on administration of DMF with acetylsalicylic acid, oral contraceptives, and vaccination with non-live vaccines (Section 4.4 and/ or Section 4.5 of the SmPC).

Post-marketing experience

Post marketing data, following approval of DRF in the US in 2019, did not alter the perception of its safety profile. Some safety signals/ potential safety concerns derived from post marketing experience with Tecfidera have not been identified in the DRF phase 3 clinical programme. These include PML, lymphopenia/ leukopenia, Herpes Zoster, drug-induced liver injury, cases of overdose, anaphylactic reactions, thrombocytopenia, and Fanconi syndrome. Given that these safety concerns have been assessed and confirmed for Tecfidera, warnings and ADRs have also been included in the proposed product information and in the RMP for DRF.

2.6.10. Conclusions on the clinical safety

Given that comprehensive safety data and post-marketing experience is available for Tecfidera, which is approved in the same indication and which results in bioequivalent exposure of MMF, it seems acceptable that the safety database of DRF is not based on pivotal trial data.

An improved GI tolerability of DRF over DMF has not been established based on the data provided for Study A302.

No unexpected safety findings have been reported with DRF when compared to the pivotal safety experience with DMF of similar treatment duration. While duration of follow-up for the Phase 3 DRF studies with a median exposure of almost 2 years limits the ability to assess some potential long-term safety outcomes, e.g., malignancies and (serious) opportunistic infections, no new concerns have been raised based on the safety results in the long-term extension Study 109MS303 (with up to 12 years exposure). However, post-marketing data for Tecfidera indicated safety signals for rare events like PML, anaphylaxis, and Fanconi syndrome that need likewise to be considered for DRF.

For AESI, for example lymphopenia, changes in renal laboratory tests (renal injury), and (drug-induced) liver injury, warnings and detailed description of these safety issues are recommended in the DRF product information in line with Tecfidera (see SmPC Section 4.4 and 4.8). These include regular monitoring and appropriate treatment discontinuation rules at defined cut-off values of laboratory assessments.

Approval of DRF can now be recommended from a safety perspective. The Pharmacovigilance Plan delineated in the RMP has been amended in line with the provided data.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 24: Summary of safety concerns

Important identified risks	• PML • Decreases in leukocyte and lymphocyte counts • DILI
Important potential risks	• Serious and opportunistic infections (other than PML and herpes zoster) • Malignancies • Effects on pregnancy outcome • Interaction with nephrotoxic medications leading to renal toxicity
Areas of missing information	• Long-term efficacy and safety • Safety profile in patients older than 65 years • Safety profile in patients with moderate to severe renal impairment • Safety profile in patients with hepatic impairment • Safety profile in patients with severe active GI disease • Increased risk of infection in patients concomitantly taking antineoplastic or immunosuppressive therapies

2.7.2. Pharmacovigilance plan

Table 25: Summary of on-going and planned additional pharmacovigilance activities

Study name and description	Summary of objectives	Safety concerns addressed relevant for DRF	Milestones	Due dates
Category 1 – ***Imposed mandatory additional pharmacovigilance activities that are conditions of the marketing authorisation***				
None				
Category 2 – ***Imposed mandatory additional pharmacovigilance activities that are specific obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances***				
None				
Category 3 – ***Required additional pharmacovigilance activities***				
Planned studies				
Vumerity (diroximel fumarate) Pregnancy Exposure Registry (272MS401)	*Primary Objective:* • To compare the maternal, foetal, and infant outcomes of women with MS exposed to DRF during pregnancy with 2 unexposed comparator populations.	• Effects on pregnancy outcomes	Final CSR	Q1/2033
Vumerity (diroximel fumarate) Registry-Based Safety Study (title pending)	*Primary Objective:* • To assess the long-term safety of DRF.	• Long-term safety profile	Pending	Pending
Ongoing studies				
Phase 3, open-label study to evaluate the long-term safety and tolerability of ALKS 8700 in adults with relapsing-remitting multiple sclerosis (EVOLVE-MS-1)	*Primary Objective:* • To evaluate the long-term safety and tolerability of DRF for up to 96 weeks of treatment in adult participants with RRMS. *Secondary Objective:* • To evaluate treatment effect over time in adult participants with RRMS treated with DRF.	• Decreases in leukocyte and lymphocyte counts • DILI • Serious and opportunistic infections (other than PML and herpes zoster) • Malignancies • Interaction with nephrotoxic medications leading to renal toxicity • Long-term efficacy and safety • Safety profile in patients with moderate to severe renal impairment	Ongoing Final CSR	Q2/2022
A Multicenter, Global, Observational Study to Collect Information on Safety and to Document the Drug Utilization of Tecfidera™ (Dimethyl Fumarate) When Used in Routine	*Primary Objective:* • To determine the incidence, type, and pattern of SAEs, including but not limited to infections (including opportunistic infections), hepatic events, malignancies, and renal events, and of AEs leading to treatment discontinuation in patients with MS treated with Tecfidera.	• Decreases in leukocyte and lymphocyte counts • DILI • Serious and opportunistic infections (other than PML) • Safety profile in patients over the age of 65 years	Ongoing Final CSR	Q4/2024

Study name and description	Summary of objectives	Safety concerns addressed relevant for DRF	Milestones	Due dates
Medical Practice in the Treatment of Multiple Sclerosis (109MS401 - ESTEEM)	*Secondary Objectives:* • To determine Tecfidera prescription and utilisation patterns in routine clinical practice in patients with MS. • To assess the effectiveness of Tecfidera on MS disease activity and disability progression in routine clinical practice as determined by the Expanded Disability Status Scale (EDSS) score and MS relapse information. To assess the effect of Tecfidera on health-related QoL, healthcare resource consumption, and work productivity.	• Safety profile in patients with renal impairment • Safety profile in patients with hepatic impairment • Safety profile in patients with severe active GI disease • Interactions with nephrotoxic medications leading to renal toxicity • Increased risk of infection in patients concomitantly taking antineoplastic or immunosuppressive therapies		

Note: A registry-based post-authorisation safety study has been added to the PhV Plan as a Category 3 study with the objective to further characterise the long-term safety of diroximel fumarate (and dimethyl fumarate), especially with regard to the important potential risks of malignancies and serious and opportunistic infections. The applicant confirmed that the study protocol will be submitted as a stand-alone procedure (MEA) within three months following approval of the marketing authorisation.

2.7.3. Risk minimisation measures

Table 26: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
PML	***Routine risk minimisation measures:*** SmPC Sections 4.4, 4.8, and PL Section 4. ***Other routine risk minimisation measure:*** Legal status: Prescription Only Medicine ***Additional risk minimisation measures:*** No additional risk minimisation measures.	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** Case reports of PML will be submitted with each PSUR and assessed using standardised criteria. Targeted follow-up questionnaire. ***Additional pharmacovigilance activities:*** None.
Decreases in leukocyte and lymphocyte counts	***Routine risk minimisation measures:*** SmPC Sections 4.4, 4.8, and PL Section 4. ***Other routine risk minimisation measure:*** Legal status: Prescription Only Medicine ***Additional risk minimisation measures:***	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** Targeted follow-up questionnaire ***Additional pharmacovigilance activities:*** Phase 3, long-term safety and tolerability of ALKS 8700 (DRF Study ALK8700-A301). Observational study (Tecfidera Study 109MS401).

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	No additional risk minimisation measures.	
Drug-induced liver injury	***Routine risk minimisation measures:*** SmPC Sections 4.4, 4.8, and PL Section 4. ***Other routine risk minimisation measure:*** Legal status: Prescription Only Medicine ***Additional risk minimisation measures:*** No additional risk minimisation measures.	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** Targeted follow-up questionnaire ***Additional pharmacovigilance activities:*** Phase 3, long-term safety and tolerability of ALKS 8700 (DRF Study ALK8700-A301). Observational study (Tecfidera Study 109MS401).
Important potential risks		
Serious and opportunistic infections (other than PML and herpes zoster)	***Routine risk minimisation measures:*** SmPC Section 4.4 and PL Section 4. ***Other routine risk minimisation measure:*** Legal status: Prescription Only Medicine ***Additional risk minimisation measures:*** No additional risk minimisation measures.	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** Targeted follow-up questionnaire ***Additional pharmacovigilance activities:*** Phase 3, long-term safety and tolerability of ALKS 8700 (DRF Study ALK8700-A301). Observational study (Tecfidera Study 109MS401).
Malignancies	***Routine risk minimisation measures:*** SmPC Section 5.3 (*Preclinical Safety*) ***Other routine risk minimisation measure:*** Legal status: Prescription Only Medicine ***Additional risk minimisation measures:*** No additional risk minimisation measures.	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** Targeted follow-up questionnaire ***Additional pharmacovigilance activities:*** Phase 3, long-term safety and tolerability of ALKS 8700 (DRF Study ALK8700-A301). Observational study (Tecfidera Study 109MS401).
Effects on pregnancy outcome	***Routine risk minimisation measures:*** SmPC Sections 4.6, 5.3, and PL Section 2. ***Other routine risk minimisation measure:*** Legal status: Prescription Only Medicine ***Additional risk minimisation measures:*** No additional risk minimisation measures.	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** None. ***Additional pharmacovigilance activities:*** Vumerity (Diroximel Fumarate) Prospective MS Pregnancy Exposure Registry (DRF Study 272MS401). Interim reports will be submitted with each PSUR.
Interaction with nephrotoxic medications leading to renal toxicity	***Routine risk minimisation measures:*** SmPC Section 4.5 and PL Section 2.	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:***

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Other routine risk minimisation measure: Legal status: Prescription Only Medicine ***Additional risk minimisation measures:*** No additional risk minimisation measures.	None. ***Additional pharmacovigilance activities:*** Observational study (Tecfidera Study 109MS401).
Areas of missing information		
Long-term efficacy and safety	***Routine risk minimisation measures:*** SmPC Sections 4.8 and 5.1. ***Other routine risk minimisation measure:*** Legal status: Prescription Only Medicine ***Additional risk minimisation measures:*** No additional risk minimisation measures.	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** None. ***Additional pharmacovigilance activities:*** Phase 3, long-term safety and tolerability of ALKS 8700 (DRF Study ALK8700-A301). Observational study (Tecfidera Study 109MS401). Registry-based safety study
Safety profile in patients over the age of 65 years	***Routine risk minimisation measures:*** SmPC Sections 4.2 and 5.2. ***Other routine risk minimisation measure:*** Legal status: Prescription Only Medicine ***Additional risk minimisation measures:*** No additional risk minimisation measures.	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** None. ***Additional pharmacovigilance activities:*** Observational study (Tecfidera Study 109MS401).
Safety profile in patients with moderate-to-severe renal impairment	***Routine risk minimisation measures:*** SmPC Section 4.4 and PL Section 2. ***Other routine risk minimisation measure:*** Legal status: Prescription Only Medicine ***Additional risk minimisation measures:*** No additional risk minimisation measures.	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** None. ***Additional pharmacovigilance activities:*** Observational study (Tecfidera Study 109MS401).
Safety profile in patients with hepatic impairment	***Routine risk minimisation measures:*** SmPC Section 4.4 and PL Section 2. ***Other routine risk minimisation measure:*** Legal status: Prescription Only Medicine ***Additional risk minimisation measures:***	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** None. ***Additional pharmacovigilance activities:*** Observational study (Tecfidera Study 109MS401).

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	No additional risk minimisation measures.	
Safety profile in patients with severe active GI disease	***Routine risk minimisation measures:*** SmPC Section 4.4 and PL Section 2. ***Other routine risk minimisation measure:*** Legal status: Prescription Only Medicine ***Additional risk minimisation measures:*** No additional risk minimisation measures.	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** None. ***Additional pharmacovigilance activities:*** Observational study (Tecfidera Study 109MS401).
Increased risk of infection in patients concomitantly taking antineoplastic or immunosuppressive therapies	***Routine risk minimisation measures:*** SmPC Section 4.5 and PL Section 2. ***Other routine risk minimisation measure:*** Legal status: Prescription Only Medicine ***Additional risk minimisation measures*** No additional risk minimisation measures.	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** None. ***Additional pharmacovigilance activities:*** Observational study (Tecfidera Study 109MS401).

2.7.4. Conclusion

The CHMP considered that the risk management plan version 1.0 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Since the major active metabolite MMF was established to be the same for diroximel fumarate as for dimethyl fumarate, diroximel fumarate should be added to the entry for dimethyl fumarate (MS) in the EURD list.

2.9. Product information

2.9.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Tecfidera and Tysabri. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

MS is a chronic autoimmune and neurodegenerative disease of the CNS characterised by inflammation, demyelination, neuronal and oligodendrocyte loss, and disruption of the blood-brain barrier, leading to irreversible deficits in physical function and cognition and an impaired quality of life. Typically, MS starts in the second or third decade of life.

RRMS is the most common form of MS, representing approximately 85% of patients at diagnosis, and it is characterised by alternating exacerbations of neurological dysfunction followed by periods of remission with partial or total recovery and clinical stability, which can last for months or years (EMA MS guideline, EMA/CHMP/771815/2011, Rev. 2).

The sought indication for this application is:

> Vumerity is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis *(see section 5.1 for important information on the populations for which efficacy has been established).*

The starting dose for diroximel fumarate is 231 mg twice a day orally. After 7 days, the dose should be increased to the recommended maintenance dose of 462 mg (administered as two 231 mg capsules) twice a day orally. Temporary dose reductions to 231 mg twice a day may be considered for individuals who do not tolerate the maintenance dose. Within 1 month, the recommended dose of 462 mg twice a day should be resumed.

3.1.2. Available therapies and unmet medical need

In addition to medicines approved for the symptomatic treatment of MS (e.g., aminopyridine for improvement of walking ability) and for the treatment of relapses (such as corticosteroids), there are currently more than 10 DMTs approved for use in patients with RRMS and/ or other forms of RMS in the EU. In a clinical setting, early treatment of relapsing MS usually starts with a substance from the IFN-beta class, GA, dimethyl fumarate or teriflunomide. These medicines are characterised by a rather moderate clinical efficacy (relative relapse reduction compared to placebo in the 30–50% range) and are therefore used in subjects without high disease activity.

A higher relative relapse reduction was found to be achieved by the S1P receptor modulator fingolimod, which is therefore approved for highly active RRMS only owing to its safety profile. Safety concerns with fingolimod include cardiac effects at treatment initiation, serious and opportunistic infections, PML,

cutaneous malignancies, lymphoma, macular oedema, posterior reversible encephalopathy, respiratory effects, increased liver enzymes and the risk of rebound after stopping the treatment.

Three drugs from the class of S1P receptor modulators have recently been approved, i.e., siponimod, ozanimod and ponesimod. Siponimod is indicated for the treatment of adults with secondary progressive MS with active disease evidenced by relapses or imaging features of inflammatory activity. Ozanimod is indicated for the treatment of adult patients with RRMS with active disease as defined by clinical or imaging features. Ponesimod is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features.

The monoclonal DMTs anti CD-20, ocrelizumab and ofatumumab are indicated for the treatment of adult patients with RMS with active disease defined by clinical or imaging features. Other DMTs include the monoclonal antibodies alemtuzumab and natalizumab, as well as cladribine, a nucleoside analogue of deoxyadenosine , which are restricted to subjects with highly active disease due to less favourable safety profiles. Daclizumab has been withdrawn from the market in 2018 due to serious safety concerns (cases of serious inflammatory brain disorders). The chemotherapeutic agent mitoxantrone is reserved for patients with high active MS without alternative treatment options.

3.1.3. Main clinical studies

This MAA includes data for both DRF and DMF. The primary evaluation of DRF efficacy is based on a PK bridging approach between DRF and DMF with respect to the common active metabolite MMF, and no placebo-controlled clinical efficacy study with typical MS disease endpoints was conducted in the DRF clinical programme. The clinical efficacy and safety package for DRF thus relies primarily on DMF data already submitted and assessed as part of the Tecfidera MAA (Tecfidera EPAR EMEA/H/C/002601/0000/Rev 1).

Vumerity (DRF) Clinical Data

The clinical programme for DRF includes ten completed Phase 1 studies and one completed and one ongoing Phase 3 studies. Of the 12 clinical studies with DRF, 11 have been completed, and one is ongoing as of the clinical cut-off date of 07 February 2020. These studies include the following:

- seven Phase 1 studies to assess the PK, ADME, DDIs, effects on cardiac repolarisation, and PK in subjects with renal impairment
- three Phase 1 studies to establish relative BA of MMF between DRF and DMF under fasted and fed conditions as well as with varying conditions of fat and caloric content
- one Phase 3, double-blind study to evaluate the comparative GI tolerability of DRF and DMF (Study A302 [EVOLVE-MS2])
- one Phase 3, open-label safety study of DRF (Study A301 [EVOLVE-MS1], ongoing)

Study A302 (EVOLVE-MS-2) was conducted in two parts (Parts A and B). Parts A and B were identical in study design and included a 5-week, DB treatment period with 2 blind treatment arms (DRF and DMF). The first 120 eligible subjects were randomised to one of the two treatment groups in Part A (n = 60 per group). Once randomisation for Part A was complete, the next 386 eligible subjects were randomised into one of the two treatment groups in Part B (194 subjects in the DRF group and 192 subjects in the DMF group).

GI tolerability was determined using the IGISIS and GGISIS. A number of secondary, exploratory and other endpoints have been also used for assessment. Typical MS disease assessments (such as EDSS, MS relapse, T25-FW, SF-12 and EQ-5D-5L) belonged to other endpoints.

The Study A302 had an adaptive design such that data from Part A could be used to modify the GI tolerability endpoints and sample size in the study. Part A was exploratory. Following completion of Part A, the applicant conducted a planned, unblinded exploratory analysis of the Part A GI tolerability and safety data to inform the endpoint selection for the overall study. The SAP was updated following the review of Part A data. This adaptive approach was taken to better inform the sample size of Part B and the overall study analysis given that the endpoints were based on exploratory GI symptom scales that were being used for the first time.

Study A301 (EVOLV-MS-1), still ongoing, attempts to evaluate the long-term safety and tolerability of DRF in adults with RRMS. In this multicentre OL study, DRF was administered up to 96 weeks for the treatment of RRMS. The target population for this study was adults, aged 18 to 65 years, diagnosed with RRMS.

DMF Clinical Data

Four DMF studies are particularly relevant in supporting the dosing, efficacy, and safety for DRF: a Phase 2 placebo-controlled dose-finding study for DMF (Study C-1900), a 2-year, placebo-controlled Phase 3 study (Study 109MS301), a 2-year, placebo-controlled Phase 3 study with an active comparator (Study 109MS302), and an open-label extension study (Study109MS303). These studies and an interim report for 109MS303 have been assessed during the MA procedure for Tecfidera (DMF).

Study 109MS301 (DEFINE)

Study 109MS301 was designed to determine the efficacy and safety of DMF in participants with RRMS. The study was a Randomized, Multicentre, DB, Placebo-Controlled, Dose-Comparison Study. Subjects were randomised in a 1:1:1 ratio to receive DMF 240 mg BID, DMF 240 mg TID, or placebo. 1011 subjects were planned, 1237 subjects were randomised, and 1234 subjects were dosed.

Study 109MS302 (CONFIRM)

Study 109MS302 was a pivotal Phase 3 Randomized, Multicentre, Placebo-Controlled, double-blind, rater-blind and Active Reference (GA) Comparison Study to Evaluate the Efficacy and Safety of BG00012 in Subjects With Relapsing-Remitting Multiple Sclerosis (RRMS). Participants were randomised in a 1:1:1:1 ratio to receive DMF 240 mg BID, DMF 240 mg TID, GA, or placebo. A total of 1232 subjects were planned, 1430 subjects were randomised, and 1417 subjects were dosed.

Study C-1900

A phase 2, randomised, multicentre, placebo-controlled, DB, parallel-group, dose-ranging study, which provided dose-response data and supported the continued development of the DMF 240 mg TID dose. The sample size for this study was 257 randomised subjects.

Study 1409MS303 (ENDORSE)

Study 109MS303 was the OLE study of the pivotal Phase 3 studies (Studies 109MS301 and 109MS302) and was ongoing at the time of the submission of the Tecfidera MAA. Interim efficacy results through 03 August 2011 were provided with the Tecfidera MAA. The final results have been submitted with this MAA.

3.2. Favourable effects

The development strategy for DRF was based upon the bioequivalent exposure levels of MMF after oral dosing of DRF 462 mg and DMF 240 mg and a PK bridging approach between DRF and DMF. Bioequivalence to DMF has been shown for the active moiety MMF. A similar food effect for both DRF and DMF could also be shown, therefore DRF can be given with instructions for intake similar to Tecfidera®.

DRF clinical efficacy data

In the short-term Study A302 for the pooled data in Parts A and B, the mean values of event days for observed diaries (i.e., all diaries collected, without imputation of any values) were 1.5 days and 2.5 days for the primary endpoint (Number of Days With Any IGISIS Symptoms Intensity Score ≥2), for the DRF and DMF groups, respectively. This was adjusted for study parts, region (US and non-US), age, and BMI and led to a rate of 0.041 for the DRF group, which was lower than the rate 0.076 for the DMF group. The rate ratio for the pooled Parts A and B was 0.542 (95% CI [0.390, 0.754]) with a corresponding p=0.0003, representing a relative reduction in GI symptoms of 45.8% in the DRF group compared with the DMF group.

After a requested imputation analysis, for the FAS population of Part B only, the mean (95% CI) number of event days for imputed diaries were 1.76 days (1.271, 2.248) and 2.51 days (1.910, 3.114) for the DRF (ALKS 8700) and DMF groups, respectively with a difference of 0.75 of a day. The rate (95% CI) obtained from the negative binomial model was 0.043 (-0.172, 0.258) for the DRF group, which was lower than the 0.070 (-0.134, 0.275) in the DMF group. The rate ratio (95% CI) was 0.609 (0.300, 0.918), with a corresponding p = 0.0132.

Statistically significant differences have been also demonstrated in the FAS population for the part B only (0.520, p=0.0007). It is noted that Part B results (key secondary endpoint) were significant and consistent with the pooled results. Results of GGISIS that were not statistically significant but all numerically favoured DRF. These differences in IGISIS and GGISIS and other secondary endpoints (e.g., Number of days with any IGISIS individual symptom intensity score ≥ 1 and ≥ 3 relative to exposure days in Part A and Part B and Worst IGISIS individual symptom intensity score by week during the 5-week treatment period in Part A and Part B) after short term treatment, could be indicative of better GI tolerability in favour of DRF compared to DMF. In the case of the exploratory and other endpoints, which were typical MS relevant endpoints, it was anticipated that no meaningful differences could be observed between the two treatments, DMF and DRF, due to the short duration of the study. However, it is noted that the two treatments (despite the short duration of 12 weeks) behaved similarly i.e. EDSS (mean and median), MS relapse, T25-FW, SF-12, EQ-5D-5L scores at baseline and their change from baseline were similar between ALKS 8700 (DRF) and DMF.

In the open label study A301, the efficacy results for clinical and MRI endpoints in participants with RRMS treated with DRF in Study A301 showed treatment effects in line with expectations from data available for DMF.

The mean change from baseline in the GdE lesions count for the De Novo group, the ALKS-8700 Rollover group, and the DMF Rollover group was -0.85, -0.49, and -0.97 lesions, respectively, which corresponds to 64.4%, 80.3%, and 80.2% decrease from baseline, respectively. Overall, there was an increase in the proportion of participants with 0 GdE lesions (20.7%) from baseline to Week 96 as well as decreases in the proportions of participants with 1 to 4, 5 to 8, and ≥ 9 GdE lesions (-14.7%, -3.8%, and -1.9%, respectively) from baseline to Week 96. Across the 3 groups, a high proportion of participants (> 90%) had 0 GdE lesions at Week 96.

The majority of subjects (84.5% [893/1057]) did not experience a protocol-defined relapse during the course of the study. The ARR for the overall Safety population was 0.14, with similar ARR values across the treatment groups.

The mean EDSS score calculated at baseline was similar across the groups. In the FAS population, the mean EDSS score in the De Novo group, the ALKS-8700 Rollover group, and the DMF Rollover group was 2.71, 2.64, and 2.71, respectively.

The proportion of subjects with confirmed disability progression sustained for 12 weeks was low in all groups, with 8.1% of subjects in the *de novo* group and 7.2% and 8.9% participants in the ALKS-8700 and DMF Rollover groups, respectively, experiencing confirmed disability progression.

DMF clinical efficacy data

In each study, both doses led to an approximately 50% reduction of the ARR relative to placebo (Study 109MS301: 53% reduction with BID and 48% reduction with TID; Study 109MS302: 44% reduction with BID and 51% reduction with TID). For the integrated analysis, DMF 240 mg BID reduced the ARR by 48.5% compared with placebo over two years of treatment.

In Study 109MS301, the estimated proportion of subjects with 24-week confirmed disability progression at 2 years was 0.169 for placebo, 0.128 for BID, and 0.119 for TID (23% reduction for BID and 31% reduction for TID relative to placebo; p = 0.1893 and 0.0760, respectively). In Study 109MS302, the estimated proportion of participants with 24-week confirmed disability progression at 2 years was 0.125 for placebo, 0.078 for BID, and 0.086 for TID (38% reduction for BID and 33% reduction for TID relative to placebo; p = 0.0630 and 0.1172, respectively).

Approximately 45% of subjects in Studies 109MS301 and 109MS302 underwent MRI brain scans. DMF led to significant and statistically robust improvements in all MRI measures of brain lesion activity for both doses in Studies 109MS301 and 109MS302.

The adjusted ARR in subjects treated with Tecfidera was low and remained stable throughout the entire treatment period in Studies 109MS301 or 109MS302 and Study 109MS303 for participants receiving DMF BID continuously.

Results from the pivotal Phase 3 Studies 109MS301 and 109MS302 demonstrated that the dose 240 mg BID of DMF consistently provided significant improvement compared with placebo in both clinical and MRI outcome measures and showed increased efficacy compared with an approved first-line therapy, GA, in participants with RRMS.

Based on the results of the bioequivalence studies and upon the similar exposure levels of MMF, DRF (after oral dosing of 462 mg) can rely on the DMF clinical study programme with an established favourable benefit/risk ratio for DMF-MMF which led to the approval for Tecfidera.

The final results of the extension study 109MS303, submitted with the MAA for DRF, confirmed the maintained treatment effect of DMF 240 mg BID with low relapse rates and confirmed disability progression for up to 12 years of treatment (duration combined with Phase 3 studies).

In the extension study (Study 109MS303), there was no evidence of diminished efficacy in reduction of ARR after an additional year (a total of 3 years) of dosing. During Study 109MS303, more than half of all participants treated with Tecfidera 240 mg BID did not have a relapse (BID/BID, 60% and placebo/BID, 66%). In Study 109MS303, 752 participants were included in an MRI cohort. Final results from extension Study 109MS303 MRI assessments showed that the majority of subjects within the MRI cohort had no GdE lesions and the number of GdE lesions remained low.

Although, OLE data should generally be interpreted with caution with regard to efficacy due to potential methodological issues, the updated and final long-term efficacy results of Study 109MS303 support the conclusion that the effect of Tecfidera and likewise of Vumerity is maintained in adult patients with RRMS.

3.3. Uncertainties and limitations about favourable effects

Design of study A302

There were differences in IGISIS and GGISIS and other secondary endpoints (e.g., Number of days with any IGISIS individual symptom intensity score ≥ 1 and ≥ 3 relative to exposure days in Part A and Part B and Worst IGISIS individual symptom intensity score by week during the 5-week treatment period in Part A and Part B), which could have been indicative of better GI tolerability in favour of DRF compared to DMF. However, the results of the study A302 cannot be considered adequate to allow inclusion of a claim in the SmPC of DRF, due to a number of deficiencies such as: validity of scales, choice of Number of Days with any IGISIS Symptom Intensity Score ≥ 2 relative to exposure days as an endpoint, robustness of statistical analyses and the lack of clinically relevant and meaningful findings (please see above in the relevant sections).

Primary endpoint of A302 (EVOLVE-MS-2)

There are several issues with the choice of scales for investigation of GI tolerability, namely the IGISIS and GGISIS scales. According to the applicant, the IGISIS is designed to assess the incidence, intensity, onset, duration, and functional impact of 5 individual GI symptoms: nausea, vomiting, upper abdominal pain, lower abdominal pain, and diarrhoea. The IGISIS was administered twice daily within nine hours of taking the study drug. The severity of each individual symptom is rated via an 11-point numeric severity rating scale, where 0 indicates no symptom and 10 indicates maximum symptom severity. If an IGISIS symptom was recorded as ongoing, only the initial intensity score was collected (i.e., logically skipped item) and the initial intensity score collected at the symptom start was carried over until symptom end. However, these scales were PROs and patients responded to the questionnaires using e-diaries. Bias could be an inherent characteristic of such a PRO compared to a more reliable clinician reported outcomes. These scales were used to perform a comparison between DMF and DRF to support a better GI tolerability for DRF.

There were uncertainties on how symptoms were recorded and counted. It has been clarified that one event day was counted when a patient recorded more than 1 symptom in a day with a symptom score ≥ 2 and similarly, one event day was counted in case a symptom ended in the afternoon and another symptom started.

Furthermore, since one day has been considered in the main analysis regardless of the number of symptoms reported above the cut-off of ≥ 2 in the same day, an analysis comparing the number of event days with 2 or 3 different symptoms score ≥ 2 in both treatment groups has been provided upon request. Since the analysis from both part A and part B cannot be considered acceptable, for only part B FAS population the difference in the Summary of number of days with at least 2 IGISIS symptoms intensity scores ≥ 2 was 0.5 between DRF and DMF in a total of approximately 35 exposure days (corresponding to approximately 1.4% of exposure days). The difference in the Summary of number of days with at least 3 IGISIS symptoms intensity scores ≥ 2 was 0.2 between DRF and DMF (~0.6% of exposure days). For the event days with at least 1 IGISIS symptoms intensity scores ≥ 2 the difference between DRF and DMF was 0.84 of a day (~2.4% of exposure days) or with appropriate imputation analysis 0.75 of a day (corresponding to ~2.1% of approximately 35 exposure days). Such small differences between the two groups, using scales of questionable validity and specificity, with results from both parts A and B and from a single Study A302, cannot be considered as an appropriate justification able to support an advantage in GI tolerability for DRF.

Using a symptom intensity score ≥ 2 the event days were quite low with 1.5 and 2.5 days for DRF and DMF, respectively. It is noted that the Number of Days with any IGISIS Symptom Intensity Score ≥ 3 is below 1 for ALKS 8700 (DRF) (0.9) for Part A and B combined and for Part B only (0.7). Even lower numbers were found for Number of Days with any IGISIS Symptom Intensity Score ≥ 4, 5 and 6, whilst these scores would have been expected to have more clinical significance. The numbers with any IGISIS Symptom Intensity Scores ≥ 3, 4, 5 and 6 are very low to draw any clinically meaningful conclusions and are questioning the clinical usefulness of these scales.

In the case of number of days any IGISIS Symptom Intensity Score ≥ 1, the results for ALKS 8700 (DRF) and DMF were 2.9 and 3.9, respectively. But the rate ratio, albeit statistically significant, was 0.714 indicating only small differences in favour of ALKS 8700 (DRF) and a potential reduction of 28.6% in the number of days any IGISIS Symptom Intensity Score ≥ 1, lower than the claimed reduction of 46% in the number of days any IGISIS Symptom Intensity Score ≥ 2.

The clinical relevance of the choice of the endpoint is still not established. One could argue that a result—driven approach was applied for the intensity score ≥2. The applicant provided a discussion as to why the Number of Days with any IGISIS Symptom Intensity Score ≥2 relative to exposure days is an appropriate endpoint to provide a clinically relevant and meaningful outcome. However, despite the argumentation, it could not be robustly demonstrated that such an endpoint was an appropriate one to provide a clinically relevant and meaningful outcome. The number of event days are very small. Even with an IGISIS symptom intensity score ≥ 2 the difference between the DRF and the DMF group was less than 1 day. Differences in the percentages of subjects with GI TEAEs and in the percentages of mean duration in days between the two groups were also very small. Additional calculations were needed in almost all analyses presented in order to show a reduction in GI AEs and an advantage in favour of DRF.

Furthermore, validation for the two scales used to show better GI tolerability of DRF compared to DMF is not available. As admitted by the applicant these two patient-assessed GI tolerability scales have not been previously used in a clinical trial setting and were tailored for DRF. The publications referred to, are using different versions of these scales.

It is acknowledged that the evaluation of GI events is not a typical assessment for management of MS and as a result, no validated scales are up to now available to measure this outcome. It is noted that IGISIS and GGISIS were adapted and have several similarities to the validated Flushing Symptom Questionnaire (FSQ). During validation of the FSQ, the percentage of days with a score above a threshold of 1 and 4 were found to significantly discriminate among groups using FSQ. However, it is still unclear what difference between the assessed therapies constitutes a minimal significant or a clinically meaningful difference for IGISIS and GGISIS. It should be noted that with respect to the approach used (by Norquist et al 2007 and Paolini et al 2008) for detecting differences in cutaneous flushing (redness, warmth, tingling and/or itching) between niacin and placebo, this did not result in any regulatory action.

Bias, increased patients' expectations and tailored modified scales (similar to a "cherry picking" approach) may have been introduced in the measurements. It is questionable whether the findings from these scales would be reproducible and consistent with another treatment for MS and able to detect differences between different treatments, either.

Finally, it is considered that the "efficacy" findings for better GI tolerability are not in accordance with the safety GI ADRs. The applicant discussed the similarities in GI tolerability ADRs from a safety perspective and the findings from the IGISIS and GGISIS scales. Even with selected additional calculations, the numbers are so small that they cannot be considered to have any clinical relevance or to be sufficient enough to detect and substantiate differences between the two treatments.

Analyses of the results of A302 (EVOLVE-MS-2)

In the IGISIS scale, if a symptom was assessed as ongoing, it was only recorded in the initial intensity score. Therefore, the applicant is asked to comment on which of the analysed parameters of the IGISIS scale allowed for the assessment of the severity of the side effects, which increased in intensity over time (A302).

In the example of the applicant, whereby a participant records an ongoing symptom of nausea in the morning diary with an intensity score of 3 and over the course of the day a new nausea symptom with a newly categorised intensity score (for example, 6) is used, may not be a true reflection of the clinical condition of the patient or the course of the symptoms. It does not truly represent the worsening or the deterioration of the symptom and may provide a false picture of the symptom, introducing a bias. The same applies to recording a lower intensity score for a symptom that improves. The assumption that the symptom is unchanged until the symptom ended or symptom severity changed appears unverifiable, it would correspond to a last observation carried forward approach and creates a potentially biased outcome.

Due to the adaptive design, endpoints and sample size of Part B in Study A302 was finalised after the unblinded data from exploratory Part A have been examined. Due to this unblinded interim analysis, after which the final version of the SAP was generated, pooling of both parts cannot be accepted as a valid procedure. The primary analysis based on pooled Part A and Part B data is not acceptable due to the unblinded interim analysis with a potential type-1 error inflation and the finalisation of the SAP after the interim analysis. The analysis of the pooled data could therefore be biased. Only Part B data should be taken into account for the efficacy conclusions with respect to all analyses.

However, due to the lack of pre-specified multiplicity procedure, the initiation of Part B after unblinding the data and the finalisation of the SAP after the interim analysis, the pooled analysis is still considered exploratory and cannot be confirmatory. Nevertheless, the pooled analysis may be regarded as supportive in a descriptive way. In any case, pooled analysis and Part B analysis result in comparable results. It should be pointed out however, that the GI tolerability primary endpoint for Study A302 was the Number of days with any IGISIS individual symptom intensity score ≥ 2 relative to exposure days in Part A and Part B combined.

The main analysis (if based on Part B data), i.e., the use of a negative binomial model for the number of days with any symptom intensity score ≥ 2 using the log number of exposure days as an offset parameter is acceptable in general. However, the analysis was not clearly specified with respect to potential additional covariates. In addition, it is not clear whether the envisaged conditional procedure where the use of the model depends on the outcome still maintains the type-1 error, although inflation may not be considerable. This may, however, not be considered as a relevant issue since the negative binomial model was finally used with the initially planned covariates. Still, in order to show robustness, the applicant provided sensitivity analyses based on the proposed Poisson model with adjustment for overdispersion and the zero-inflated negative binomial model.

Furthermore, as the covariates were not properly pre-specified in the SAP (and age was added as an additional covariate), the analysis cannot be considered as fully pre-specified. The applicant provided an analysis without the factor age as a covariate as well as additional sensitivity analyses with added relevant baseline covariates. The results from the provided sensitivity analyses were consistent with the primary analysis.

The main issue in the analysis is based on the improper handling of missing evaluable diaries. For a considerable number of days the diaries were not evaluable or valid, which may also include completely missing diaries. Missing data imputation was neither planned nor performed for these days. Basically, the analysis was based on the assumption that the absence of a valid diary (or evaluability of a diary) was completely at random and the actual endpoint refers to a mixture of the presence of relevant symptoms (≥ 2) and the evaluability of the diary. Hence, the applicant attempted to justify the validity

and robustness of the conclusions with respect to the large number of non-evaluable diaries and demonstrate whether the actual analysis yields an unbiased estimation for the relative reduction in days with any symptom intensity score ≥ 2, if all diaries were evaluable.

The robustness of the analysis regarding the large amount of non-evaluable diaries was initially unclear, especially since a reference based multiple imputation approach was apparently not followed. The applicant was requested to provide a reference based multiple imputation approach that uses the data from the reference group only to generate the distributions to be used for multiple imputation. It appeared that the first reference-based multiple imputation may have not been performed properly. A multiple imputation would require the combination of multiply imputed datasets applying Rubin's rule. The applicant finally provided the requested analysis. It is noted that the point estimate of the rate ratio increased slightly, but the confidence interval got much larger and the p-value increased likely due to the increased variability of the multiple imputation approach although the result remained statistically significant.

Mechanism and potential plausibility for better GI tolerability

The mechanism for better DRF GI tolerance compared to DMF and the clinical relevance of the results in Study A302 was discussed (please see above in the relevant sections).

Among the likely reasons for better gastrointestinal-related tolerance were the lower concentration of methanol formed, the larger particle size of DRF limiting binding to receptors within the gastrointestinal tract, and the lower electrophilicity of DRF. These reasons are all speculative. There is no evidence to support that any of the presented mechanisms are important in the hypothesised better tolerance of DRF.

A301 (EVOLVE-MS-1)

The results from Study A301, albeit showing similar efficacy between DRF and DMF, both in terms of MRI and clinical efficacy endpoints, are from an open-label, single arm, long term, primarily, safety study and are not final. Hence the results should be interpreted with caution.

Paediatric data

There are no data for DRF in the paediatric population. There are very limited data for DMF in the paediatric population in a total of 34 patients, aged 13-18 years old (completed studies: 109MS202 and its extension 109MS311). These limited data collected after administration of DMF are not considered useful information to be included in the SmPC of DRF.

3.4. Unfavourable effects

TEAEs after DRF administration were reported by 88.2% and 78.3% of patients in Studies A301 and A302, with discontinuations due to TEAEs in 8% and 1.6% of patients and SAEs in 11.4% and 1.6% of patients. TEAEs with DRF in Study A301 were qualitatively and quantitatively in line with those after DMF administration in study A302 and in the Tecfidera clinical studies. The SOC with the highest proportions of subjects reporting TEAEs in A301 were infections and infestations, nervous system disorders, vascular disorders, and gastrointestinal disorders. The most common TEAEs (occurring in > 10% of patients) in study A301 included flushing (27.2%), MS relapse (19%), URTI (14.3%), nasopharyngitis (12.9%), lymphopenia (11.2%), and diarrhoea (10.3%). In study A302, TEAEs were reported most frequently in the SOCs of gastrointestinal disorders, vascular disorders, and skin and subcutaneous tissue disorders. The most commonly reported TEAE was flushing (36.7% of patients overall), followed by diarrhoea (18.8%) and nausea (17.7%).

Serious and opportunistic infections (other than PML and herpes zoster) are a potential risk with DRF treatment. In Study A301, opportunistic infections (i.e., candidiasis and candida infections) were reported in 0.6% of patients but none was serious or associated with lymphopenia. The TEAEs of oral candidiasis and candida infection were rated related to DRF and all resolved by the clinical cut-off date except for the TEAE of candida infection. Serious infections were reported by 0.9% of patients (including appendicitis, cellulitis, urinary tract infection, chronic gastritis, pharyngitis, pneumonia bacterial, pneumonia, and sepsis). One serious infection (pneumonia bacterial) resulted in discontinuation from treatment and was fatal.

Decreases in leukocyte and lymphocyte counts are an important identified risk with DRF consistent with DMF, starting at Week 4 through Week 48 with a plateau up to Week 96. Mean decreases from baseline were in the same magnitude as with DMF, i.e., 11% and 30% for leukocyte and lymphocyte counts, respectively. In A301, 42.4% of subjects had lymphocyte counts below LLN ($< 0.91 \times 10^9$/L). Half of them experienced Grade 2 lymphopenia ($< 0.8 \times 10^9$/L to 0.5×10^9/L) with an infection SAE reported in four subjects. 13.7% of *de novo* subjects, 16% of rollover subjects treated with DRF and 11.1% of rollover patients treated with DMF had moderate prolonged lymphopenia for six months. 8.7% and 0.2% of patients had Grade 3 and Grade 4 lymphopenia. Severe prolonged lymphopenia defined as ALC $< 0.5 \times 10^9$/L for more than 6 months has not been reported in A301 given that patients with lymphocyte counts $< 0.5 \times 10^9$/L for ≥ 4 weeks were to discontinue DRF according to the protocol. 16.7% of patients reported a TEAE in the lymphopenia category (i.e., lymphopenia and lymphocyte count decreased), mainly mild or moderate in severity and rated related to DRF. None of the events was serious. Events were reported with a similar incidence in the first and second year of treatment. In less than half of the subjects, lymphopenia did not resolve by the data cut-off. Less than 2% of all subjects interrupted or discontinued treatment with DRF due to lymphopenia. 0.8% of all patients reported TEAEs in A302 (DRF: 0.4%, DMF: 1.2%).

PML is classified as an important identified risk of DRF treatment in line with DMF and lymphopenia is known to increase this risk. So far, 12 cases of PML have been confirmed in DMF-exposed subjects with lymphocyte counts below LLN ($< 0.91 \times 10^9$/L); one case occurred in study 109MS303, while the remaining 11 cases occurred in the post marketing setting with Tecfidera. Two cases of PML were fatal. No case of PML was reported in the DRF clinical study programme. The risk for PML is detailed in the product information for DRF in line with DMF.

Malignancies were reported in 0.5% and pre-malignant conditions were reported in 0.7% of subjects in Study A301. A similar pattern of malignancies was observed as with Tecfidera. No such events were reported in Study A302.

Liver injury has been assessed as AESI with DRF treatment given that animal data identified liver toxicity with DMF. Increases in liver transaminases and related hepatic events have been reported in the DMF clinical programme. Drug-induced liver injury is an important identified risk with DMF and DRF and is included as ADR in Section 4.8 of the SmPC. Transient asymptomatic increases in liver transaminases with DRF were reported within the first 4 weeks of treatment in line with DMF. In a majority of subjects, increases were in line with ALT and/ or AST of < 3x ULN. Abnormalities of ALT and/ or AST > 3x ULN, > 5x ULN, and > 10x ULN occurred in no more than 2% of subjects. TEAEs of liver injury, mainly mild or moderate in severity, were reported in 7.2% of patients in Study A301 and most frequently within the first 6 months of treatment. The most commonly reported TEAEs were laboratory abnormalities, i.e., ALT increased (5.5%) and AST increased (2.9%), and ADRs are included in SmPC Section 4.8. All other events (also including cholestatic liver injury, hepatic steatosis, and hepatosplenomegaly) were each reported in ≤ 0.5% of patients. In a majority of patients, the events were related to DRF treatment and resolved. In few patients, hepatic events were serious or led to discontinuation of DRF. Hepatic TEAEs were reported in 5.4% of subjects in Study A302, with similar frequencies in the DRF and DMF group.

ALT and bilirubin increases in line with Hy's law were not observed with DRF. Baseline and routine monitoring of liver enzymes is detailed in the SmPC. Moreover, the safety profile in patients with hepatic impairment is an area of missing information in the RMP.

Preclinical studies specified the kidney as a target organ for DMF-toxicity, which likewise applies to DRF. However, DMF was not found to be associated with an increased risk for renal injury. There was no evidence for an impaired renal function with DRF treatment in Studies A301 and A302. Abnormal urinalysis parameters were reported for urine protein, urine ketones and urine occult blood (in 76.6%, 55.3%, and 37.4% of all patients in study A301) without corresponding to renal TEAEs. 3.4% of patients in A301 had a TEAE from the renal injury AESI category with proteinuria reported in a majority of them. 1.6% of subjects (with similar frequencies for DRF and DMF) reported TEAEs (mainly proteinuria) in A302. Proteinuria is included as common ADR with DRF and DMF in Section 4.8 of the SmPC. In addition, evaluation of DRF safety in subjects with normal eGFR and eGFR indicative of mild renal impairment in Study A301 did not suggest clinically significant differences. However, DRF treatment of subjects with moderate and/ or severe renal impairment is a missing information in the RMP. In addition, the interaction with nephrotoxic medications leading to renal toxicity is listed as an important potential risk in the RMP for DRF in line with DMF, which is based on the results of a subgroup analysis within the placebo-controlled DMF studies, i.e., an increased incidence of renal and urinary AEs (primarily proteinuria) in patients with concomitant potentially nephrotoxic medication.

Gastrointestinal disorders TEAEs (mainly diarrhoea, nausea, and abdominal pain) are among the most frequently reported side effects of DMF-containing drug products, with incidences between 33% (in Study 109MS303) and 48% (in Pool A) for DMF 240 mg BID and in line with data deriving from the psoriasis indication (see EPAR of Skilarence EMEA/H/C/002157/0000). Reporting of GI disorders TEAEs with DRF in line with DMF was highest during the first three months of treatment and resolved in a majority of subjects within one week. In A301, 31.6% reported GI disorders TEAEs, and 0.9% of subjects reported serious GI disorders. 1.8% of subjects had a dose reduction/ interruption due to GI events. In Study A302, 34.8% of patients in the DRF group and 49% of subjects in the DMF group reported GI disorders TEAEs. Gastrointestinal tolerability has been designated as AESI, for which only SAEs and AEs leading to discontinuation were taken into account. GI AESIs in A301 were reported in 0.8% of patients and in A302, these events were reported more frequently in the DMF group vs. the DRF group (4.8% vs. 0.8%), all of them leading to discontinuation. Routine risk minimisation measures to improve GI tolerability with DRF (like with DMF) include temporary dose reduction to half the maintenance dose and the intake with food.

TEAEs of anaphylaxis and angioedema, both of which have been reported following Tecfidera administration in the post-marketing setting, were not reported during the DRF studies.

Four deaths were reported in the DRF clinical programme, all in Study A301 (due to pneumonia bacterial, fall, hypertensive heart disease, and cardiac arrest). None of the event was rated related to DRF.

A total of ten pregnancies occurred in the DRF studies, with an outcome reported for eight pregnancies, including four full-term healthy infants; two elective abortions (at eight and ten weeks of gestation); and two spontaneous abortions. None of the pregnancies was indicative of foetal abnormalities. The impact of DRF on pregnancy outcomes will be evaluated in a prospective pregnancy registry cohort study (272MS401). Effects on pregnancy outcome is listed as an important potential risk for DRF.

3.5. Uncertainties and limitations about unfavourable effects

Long-term safety

Clinical safety of DRF primarily relies on DMF data (Tecfidera EPAR EMEA/H/C/002601/0000/Rev 1), which is based on the principle of equivalent exposure to MMF after administration of DRF 462 mg BID and DMF 240 mg BID. DRF product-specific safety data are available for 1071 subjects, who have received DRF in the two Phase 3 studies A302 and A301. The short duration of study A302 (5-weeks, including a 1-week titration to the final DRF/ DMF dose) hampers evaluation of a number of important but rare safety issues, which commonly appear with longer treatment duration (i.e., AEs due to the immunosuppressive effect of DRF, for example lymphocytopenia, opportunistic infections, and malignancies).

Study A301 covers a longer treatment duration (up to 96 weeks); however, with known limitations of an open-label design. As of the updated data cut-off 01 September 2020, 65.4% (388/593) of subjects in the *de novo* group had ≥ 24 months of cumulative treatment exposure, and 33.5% (80/239) of subjects in the DRF and 35.6% (80/225) of subjects in the DMF Rollover group, respectively, had ≥ 24 months of exposure. No unexpected findings derived from these additional safety data. 152 of 1057 subjects (14.4%) were ongoing in A301 after the updated data cut-off. Long-term safety data have also been collected for DMF in the extension study 109MS303, which likewise informs on long-term safety with DRF. The outcome of the assessment of this study for DMF will also be reflected in the DRF product information.

Safety in special population

The safety profile of DRF in the treatment of subjects with RRMS has been evaluated in subjects 18 to 65 years of age with no data available for paediatric subjects (< 18 years of age) and limited data for those with a screening age of 65 years in the phase 3 trials. 139 (13.2%) of patients in A301 were > 55 years of age, with three patients aged 65 years at baseline. Although, preliminary DRF data from A301 do not indicate a different safety profile in the elderly, pivotal DMF source data are only available and thus in support of DRF safety for patients up to 55 years of age. Remaining uncertainty in the safety profile in subjects between 55 and 65 years of age with DRF has been addressed. Analysis of demographics, TEAEs, SAEs and TEAEs leading to discontinuation in patients <55 years of age (N=899) vs. ≥55 years of age (N=158) did not reveal significant differences in the safety profile except for numerical differences in lymphopenia AEs. Adequate wording is now included in Section 4.2 of the SmPC.

The safety profile of DRF has been evaluated in patients aged 18 to 65 years. No or insufficient safety data are available for paediatric subjects (< 18 years of age) and elderly subjects (> 65 years of age). The safety profile in patients > 65 years is a missing information in the RMP.

Uncertainty has been raised with regard to the outcome of three pregnancies reported in the DMF Study 109MS303 (currently handled in the ongoing variation procedure EMEA/H/C/002601/II/0069/G), i.e. induced abortion due to congenital abnormalities, for which the narratives were insufficient to rule out a causality with DMF treatment. The rate of congenital abnormalities in study 109MS303 appears to exceed the background prevalence rate of a reference population in EUROCAT. No immediate action derives from these three cases. However, a cumulative review of pregnancies and their outcome against the background rate in EUROCAT has been requested as part of the next PSUR for DMF, which is at the time of this assessment under evaluation in EMEA/H/C/PSUSA/00010143/202103. Congenital abnormalities were not observed in placebo-controlled clinical Phase 3 studies with Tecfidera and were also not observed in the DRF clinical studies.

Uncertainty has also been raised regarding the pharmacologically inactive metabolite HES due to its accumulation with increasing renal impairment. A summary of nonclinical and clinical data could demonstrate that HES is biologically inactive and pharmacologically inert. The safety profile is found comparable in subjects with renal impairment and those with normal renal function.

A number of safety signals or potential safety concerns derived from post marketing experience with DMF but have not been observed with DRF in clinical studies. These include – amongst those listed previously - Herpes Zoster, cases of overdose, thrombocytopenia, and Fanconi syndrome. Warnings and ADRs have been included in the DRF product information.

Adverse events (of special interest)

The clinical relevance of the difference in reporting of the most common GI tolerability events (i.e., diarrhoea, nausea, abdominal pain upper, abdominal pain, and vomiting) and discontinuations due to GI events as well as GI AESI in the DRF versus the DMF group in Study A302 is uncertain because:

- the difference is based on a 5-week treatment duration in A302 (including a 1-week titration to the full dose),
- GI events do not appear to be different for DRF and DMF based on longer treatment durations in study A301 (DRF: 31.6%) and in 109MS303 (DMF: ~30% up to the data cut-off 03 August 2011 and 35% up to the data cut-off 08 November 2019).

An increased risk for infections, mainly serious and opportunistic infections is a clinically significant consequence of lymphopenia, especially if it is severe and prolonged. A relation between minimum post-baseline lymphocyte counts and the occurrence of infections was not detected in additional analyses performed for the DMF phase 3 studies; however, such a relation cannot be excluded for DRF given that ALC < $0.5x10^9$/L persisting for > 4 weeks led to discontinuation from treatment. Moreover, not only severe but also mild and moderate lymphopenia has been identified as risk factor in a total of 12 PML cases confirmed for DMF so far. Eleven of these cases occurred in the post marketing setting given that PML due to its rarity is not expected to be reported in clinical trials.

In this context, uncertainty is raised on the recovery of lymphocyte counts after discontinuation of DRF treatment (in line with DMF treatment). Subjects, who completed Study A301 or who terminated early with a last measured lymphocyte count < 0.8×10^9/L were followed up every 2 months for a maximum of 3 visits or until lymphocyte counts reached normal limits (≥ $0.91x10^9$/L). Recovery of lymphocytes was not complete for all of the 85 subjects included within the observation period, i.e., within a maximum of 6 months. This is supported by data on lymphocyte recovery in 109MS303 (currently under evaluation in EMEA/H/C/002601/II/0069/G). Results indicate that ALC in more than half of these patients recovered to ≥ LLN within the follow-up period (up to 48 weeks) in patients with ALC < LLN and ALC < $0.8x10^9$/L at recovery baseline. These data did not include subjects with severe prolonged lymphopenia (i.e., ALC < $0.5x10^9$/L for more than 6 months). A number of uncertainties have been identified for the datasets and statistical analysis underlying this evaluation and further information has been requested. Given that the applicant proposes lymphocyte count reconstitution data to be included in Sections 4.8 and 5.1 of the SmPCs for Tecfidera and Vumerity, these discrepancies have to be solved before concluding on a wording, which has been confirmed by the applicant.

While no concern for DRF over DMF is raised on the risk for malignancies based on DRF study data, this long-term risk with DMF treatment has been followed in Study 109MS303; as a consequence, additional analyses on malignancies and background rates also focussing on skin cancers have been requested as part of the most recent PSUR, which is evaluated in EMEA/H/C/PSUSA/00010143/202103 at the time of this assessment. Depending on the outcome and in line with class effects of DMTs, amendments to the product information could become necessary, which are also relevant for DRF. Malignancies have been included in the list of potential risks associated with DRF in line with DMF.

3.6. Effects Table

Table 27: Effects table for Vumerity for the treatment of adult patients with relapsing-remitting multiple sclerosis (data cut-off: 01 September 2020).

Effect	Short Description	Unit	DRF	DMF	Placebo	Uncertainties/ Strength of evidence	References
Favourable Effects							
Geometric mean ration (90% CI) for $AUC_{0\text{-last}}$ $AUC_{0\text{-}\infty}$ C_{max}	Demonstration of bioequivalence (BE) following a Single Oral Administration of 462-mg ALKS 8700 DR (Test) Versus 240-mg DMF (Reference)	(h•µg/mL) (h•µg/mL) (µg/mL)	3.38 3.57 1.57	3.14 3.56 1.67		SoE: both DRF and DMF undergo rapid presystemic hydrolysis to the active metabolite component MMF – BE demonstrated $AUC_{0\text{-last}}$: 1.08 (1.00, 1.16) $AUC_{0\text{-}\infty}$: 1.00 (0.88, 1.14) C_{max} : 0.94 (0.82, 1.07)	(BE Study A103)
IGISIS Symptom Intensity Score ⩾ 2, adjusted rate Pooled Parts A and B	Adjusted rate of number of Days With Any IGISIS Symptom Intensity Score ⩾ 2, Observed Diaries Pooled Parts A and B		0.041 (0.032, 0.053)	0.076 (0.059, 0.097)		SoE: rate ratio **0.542** (0.390, 0.754), p=0.0003 Uncertainty: primary endpoint and design with unblinded interim analysis	(2)
IGISIS Symptom Intensity Score ⩾ 2, adjusted rate (FAS Population, Part B)	Adjusted rate of number of Days With Any IGISIS Symptom Intensity Score ⩾ 2, Observed Diaries Part B only		0.033 (0.025, 0.043)	0.063 (0.049, 0.082)		SoE: rate ratio **0.520** (0.356, 0.760), p=0.0007 blinded data	(2)
IGISIS Symptom Intensity Score ⩾ 2, adjusted rate (FAS Population, Part B)	Adjusted rate of number of Days With Any IGISIS Symptom Intensity Score ⩾ 2, Observed Diaries Part B only (after multiple imputation analysis)		0.043 (-0.172, 0.258)	0.070 (-0.134, 0.275)		SoE: rate ratio **0.609** (0.300, 0.918), p=0.0132 blinded data	(2) and Day 195 responses

Effect	Short Description	Unit	DRF	DMF	Placebo	Uncertainties/ Strength of evidence	References
Proportion relapsing	Proportion of relapsing participants over 2 years			0.270 p < 0.0001 (BID) 0.260 p < 0.0001 (TID)	0.461		(3)
ARR	Annualised Relapse Ratio (rate of clinical relapses at 2 years)			0.224 p < 0.0001 (BID) 0.198 p < 0.0001 (TID)	0.401	SoE: GA 0.286 p = 0.0128[b]	(4)
Adjusted ARR	During the overall 109MS303 study period, the adjusted ARR (95% CI)			range from **0.126** (0.098, 0.162) to **0.185** (0.129, 0.265)		Uncertainty: open label single arm study	(6)
EDSS	proportion of participants who progressed			range from 21% to 37%		Uncertainty: open label single arm study	(6)
Unfavourable Effects							
Serious and opportunistic infections (other than PML and Herpes Zoster)	Number of patients with SAEs Number of patients with OIs	% %	0.9 (1) 0.6 (1)	2.0 (5) 0 (5)	1.0 (5) 0 (5)	A firm conclusion on a relation of (serious or opportunistic) infections and severe prolonged lymphopenia cannot be drawn for DRF given that ALC < $0.5x10^9$/L persisting for > 4 weeks led to discontinuation from treatment; serious and opportunistic are a potential risk in the RMP	(1), (5)
Lymphopenia (incl. lymphopenia and lymphocyte count decreased) - Grade 1 - Grade 2 - Grade 3 - Grade 4	Number of patients with TEAEs	%	16.7 (1) 0.4 (2) 9.8 (1) 22.6 (1) 8.7 (1) 0.2 (1)	1.2 (2)		Decreases in leukocyte and lymphocyte counts are a potential risk in the RMP; uncertainty on recovery of lymphocyte counts regarding presentation of data in study A301 (n=60 patients with LM follow-up and study 109MS303 (currently under evaluation in EMEA/H/C/002601/II/0069/G)	(1), (2)

Effect	Short Description	Unit	DRF	DMF	Placebo	Uncertainties/ Strength of evidence	References
Malignancies and pre-malignant conditions	Number of patients with TEAEs	%	0.5 (1) 0.7 (1)	3.0 (6)		Additional analyses on malignancies and background rates have been requested in the ongoing variation EMEA/H/C/002601/II/0069/G on 109MS303 with focus on skin cancers. Malignancies are a potential risk in the DRF RMP in line with DMF.	(1), (6)
Liver injury (mainly ALT increased and AST increased) - ALT >3x ULN - ALT >5x ULN - ALT >10x ULN	Number of patients with TEAEs	%	7.2 (1) 5.9 (2) 2.0 (1) 0.9 (1) 0.2 (1)	4.8 (2)		DILI is a potential risk with DRF treatment in line with DMF; The safety profile in patients with hepatic impairment is missing information in the RMP	(1), (2)
Renal injury (mainly proteinuria)	Number of patients with TEAEs	%	3.4 (1) 1.2 (2)	2.0 (2)		Interaction with nephrotoxic medications leading to renal toxicity (potential risk in the RMP)	(1), (2)
Gastrointestinal disorders	Number of patients with TEAEs Number of patients with SAEs Number of patients with TEAEs leading to discontinuation	% % %	31.6 (1) 34.8 (2) 0.9 (1) 0 (2) 2.2 (1) 0.8 (2)	49.0 (2) 40 (5) 35 (6) 0 (2) 1 (5) 2 (6) 5.2 (2) 4 (5) 4 (6)	31 (5) <1 (5) <1 (5)	DRF GI tolerability assessment is mainly based on study A302, with several limitations (e.g. a short 5-week treatment duration, including a 1-week titration to the full dose); GI events do not appear different for DRF and DMF based on longer treatment durations in study A301 and in 109MS303	(1), (2), (5), (6)
PML	Confirmed cases	No.	0 (1,2)	12 (6,7)		PML is an important identified risk with DRF in line with DMF; owing to its rarity, it is not expected to be observed during a clinical trial; only one confirmed case of PML so far reported in a clinical study with DMF (109MS303); 11 cases occurred in the post-marketing setting	(1), (2), (6), (7)

Abbreviations: ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BID: twice daily; DILI: drug-induced liver injury; DMF: dimethyl fumarate; DRF: diroximel fumarate; LM: lymphocyte monitoring; OI: opportunistic infections; OL: open-label; SAE: serious adverse event; TEAE: treatment-emergent adverse event; ULN: upper limit of normal

Notes: (1) DRF study A301, (2) DRF study A302, (3) Tecfidera study 109MS301, (4) Tecfidera study 109MS302 (5) Tecfidera safety Pool A, (6) Tecfidera long-term extension study 109MS303, (7) Tecfidera post-marketing experience

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Since comparative exposure to the common active metabolite MMF from 240 mg of DMF and 462 mg of DRF has been shown, the efficacy results from the DMF clinical programme can be used to support efficacy claims for DRF in the same indication, RRMS, and inform dosing. Both prodrugs and DRF undergo rapid presystemic conversion to monomethyl fumarate (MMF). The pivotal data (from Studies C-1900, 109MS301 and 109MS302) together with other supportive studies justified the approval of Tecfidera (DMF) in RRMS (reference is made to EMEA/H/C/002601/0000/Rev 1). Hence, it can be assumed that DRF will have similar efficacy in comparison to DMF in patients with RRMS. Results from an open label long term study still ongoing are indicative of the similarity of efficacy of DMF and DRF.

However, the claim for additional benefit of improved GI tolerability has not been robustly demonstrated. There are several issues with the design, choice of primary endpoint and scales for assessing GI tolerability and the analyses of the results in the study used for supporting better GI tolerability of DRF compared to DMF. Data to support the underlying hypothesised mechanisms for better GI tolerance for DRF were not provided.

The overall safety database including product-specific DRF safety data from two Phase 3 studies together with DMF controlled safety data from two pivotal studies (reference is made to EMEA/H/C/002601/0000/Rev 1) and long-term safety data from an 8-year extension study in the treatment of adult subjects with RRMS is considered comprehensive. As per the cut off 01 September 2020, 912 subjects (86.3%) and 548 subjects (51.8%) received DRF for more than 12 months and 24 months, respectively. In addition, MS integrated clinical study experience with Tecfidera as per the latest available data cut-off 26 March 2020 added 1872 and 1604 subjects with exposure to DMF for 1 year and 2 years, respectively, and 426 and eight subjects with exposure to DMF for 10 years and 12 years, respectively.

The safety profile of DRF is qualitatively and quantitatively in line with that of DMF. No unexpected safety issues have been identified for DRF.

The main tolerability issues of DRF and DMF treatment, i.e., flushing and GI events can be mitigated by the initial 7-day dose titration with half the maintenance dose at Day 1 (i.e., 231 mg DRF BID), which is to be increased to the full dose on Day 7 (i.e. 462 mg DRF BID). Moreover, administration with food was found to reduce tolerability issues with DMF (see Section 4.2 of the product information for Tecfidera), which similarly applies to DRF. Tolerability events that occur intermittently are manageable by temporary dose reduction.

Improved GI tolerability has not been robustly demonstrated for DRF over DMF. Although, it appears that GI tolerability events are less frequently observed with DRF as compared to DMF and that such events are less often serious or leading to discontinuation of treatment, this is based on a short-term comparison between DRF and DMF in Study A302. Moreover, no clinically relevant difference in the occurrence of GI events can be observed with longer DRF treatment duration as compared to DMF (based on the uncontrolled studies) and GI events are known to occur intermittently during treatment. Product-specific GI data on DRF have been summarised in Section 5.1 in the SmPC.

AESI, i.e., decreases in lymphocyte and leukocyte counts, as well as renal and hepatic injury, were found to be manageable by routine clinical and laboratory monitoring and treatment discontinuation, as appropriate. Information and warnings are adequately included in the product information and the potential risks and areas of missing information have been included in the RMP of DRF in line with DMF.

The risk for opportunistic and serious infections (other than PML and Herpes Zoster) is adequately covered in the product information. Monitoring for signs and symptoms of infection is recommended and treatment should be suspended in case of a serious infection. Moreover, patients with a serious infection should not start treatment. Similarly, it cannot not be ruled out that rare opportunistic infections like PML might occur in the presence of moderate to severe prolonged lymphopenia. Additional risk minimisation measures for the prevention of PML have been introduced for DMF following the 7th confirmed case of PML in a patient with transient, mild lymphopenia in the post marketing setting (EMEA/H/C/2601/II/63). These include a contraindication in patients with suspected or confirmed PML, detailed warnings (stopping rules, additional factors that might increase the risk for PML and demand increased vigilance), and description of study findings for lymphocyte subsets in Section 4.8. These warnings are likewise included in the DRF PI.

Limitation of safety data in the elderly has been addressed and the age cut-off of 65 years for DRF (contrasting the age cut-off for Tecfidera of 55 years of age) has been justified based on a comparison of the safety profile in patients between 55 and 65 years of age and patients < 55 years of age. No worsening of the safety profile could be deduced from this comparison in patients > 55 years of age.

Long-term safety of DRF has been further investigated in the ongoing Study A301 for which the final CSR is expected in Q2/2022. Thus, updated information on clinical safety as per the data cut-off 01 September 2020 does not raise additional concerns. Nevertheless, 14.4% of subjects are still ongoing. Given the extent of comparability between DRF and DMF, the long-term safety experience with Tecfidera is relevant and supporting. Some uncertainties about the unfavourable effects of long-term DRF treatment derive from long-term treatment with DMF in Study 109MS303 and the outcome of its assessment in the ongoing variation procedure EMEA/H/C/2601/II/0069/G will inform the safety conclusions on DRF and the labelling in the product information. These include:

- additional information on recovery of lymphocyte counts after discontinuation of DMF with uncertainty on the datasets underlying this evaluation,
- 3 cases of congenital malformations; no such cases have been reported with Tecfidera in clinical studies so far. Like Tecfidera, Vumerity should be used during pregnancy only if clearly needed and if the potential benefit justifies the potential risk to the foetus. No immediate action derives from these cases.
- the long-term risk for malignancies with DMF treatment; although, the incidence did not increase with long-term treatment, a causal relationship can neither be established nor ruled out based on the available clinical data. Additional analyses on malignancies and background rates have been requested in with focus on skin cancers.

The applicant confirmed that the product information will be updated to reflect the outcome of EMEA/H/C/2601/II/0069/G.

Additional long-term data for DMF will be provided in the context of the PASS study 109MS401, a multicentre, global, observational study collecting information on safety and drug utilisation of Tecfidera when used in routine medical practice, for which the final CSR is expected in Q4/2024. This study aims to address the potential risks and missing information associated with DMF, for which the results are also applicable to DRF given that the same potential risks and area of missing information apply.

A further registry-based Category 3 study with the objective to further characterise the long-term safety of diroximel fumarate (and dimethyl fumarate), especially with regard to the important potential risks of malignancies and serious and opportunistic infections, has been added to the Pharmacovigilance Plan for DRF. The applicant committed to submit the study protocol as a stand-alone (MEA) procedure following approval of the marketing authorisation. Study details, including data sources, objectives, and milestones will be specified in that MEA procedure.

3.7.2. Balance of benefits and risks

In terms of clinical efficacy, the benefit for DRF relies on bioequivalent exposure levels to the principle active moiety MMF, which is the same for DMF and DRF and consequently the efficacy and systemic safety results from Tecfidera (DMF) can be extrapolated to Vumerity (DRF). The investigation of GI tolerability yielded some statistically significant results with questionable design, primary endpoint and analyses. The differences in GI adverse events were so small that they cannot be considered clinically relevant. Hence it cannot be considered that a better GI tolerability profile of DRF compared to DMF has been demonstrated.

The safety profile of DRF in the proposed indication "treatment of adult patients with relapsing remitting multiple sclerosis" did not present with any unexpected findings as compared to DMF, which was authorised in the EU more than 7 years ago. The RMM proposed for DRF have proven to be efficacious for DMF.

The amount of clinical trial data and post-marketing experience with DMF appears reassuring that the safety of DRF is likewise manageable with the same precautionary measures in place in the product information and post-authorisation safety measures.

Despite tolerability issues mainly occurring during initiation of DRF therapy, there are safety concerns to be considered with chronic DRF use in line with DMF, i.e., pronounced lymphopenia that increases the risk for serious/ opportunistic infections, including PML, but also DILI. The determination of the long-term safety risks is still outstanding and will be further addressed in the ongoing DRF Phase 3 study A301 and in the observational drug utilisation Study 109MS401 with DMF.

Approval can be recommended.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall benefit/risk balance of Vumerity is positive, subject to the conditions stated in Section 5 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Vumerity is favourable in the following indication(s):

> Vumerity is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (see section 5.1 for important information on the populations for which efficacy has been established).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

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

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

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

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

Not applicable.