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APPLICATION NUMBER:

210296Orig1s000

CLINICAL REVIEW(S)

Clinical Review
Paul Lee, M.D., Ph.D.
NDA-210296
Bafiertam (monomethyl fumarate)

CLINICAL REVIEW

Application Type	505(b)(2)
Application Number(s)	NDA-210296
Priority or Standard	Standard
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Division/Office	Division of Neurology Products
Reviewer Name(s)	Paul Lee, M.D., Ph.D.
Review Completion Date	October 31, 2018
Established/Proper Name	Monomethyl fumarate
(Proposed) Trade Name	Bafiertam
Applicant	Banner Life Sciences
Dosage Form(s)	95 mg delayed release oral capsule
Applicant Proposed Dosing Regimen(s)	Starting dose: 95 mg twice a day, orally, for 7 days Maintenance dose after 7 days: 190 mg twice a day, orally
Applicant Proposed Indication(s)/Population(s)	Bafiertam is indicated for the treatment of patients 18 years and older with relapsing forms of multiple sclerosis (RMS)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Patients ages 18 and older with Relapsing Forms of Multiple Sclerosis (RMS)

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CNS	Central Nervous System
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
DMF	Dimethyl Fumarate
DR	Delayed Release
ECG	Electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GI	Gastrointestinal
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat

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LLN	Lower Limit of Normal
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MMF	Monomethyl Fumarate
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
Nrf2	Nuclear factor (erythroid-derived 2)-Related Factor 2
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PML	Progressive Multifocal Leukoencephalopathy
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PT	Preferred Term
REMS	risk evaluation and mitigation strategy
RMS	Relapsing forms of Multiple Sclerosis
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
WBC	White Blood Cell

1. Executive Summary

1.1. Product Introduction

Monomethyl fumarate (Bafiertam, BLS-11, or MMF) is the primary active metabolite of dimethyl fumarate (Tecfidera, BG-12, or DMF), an approved therapy for the treatment of relapsing forms of multiple sclerosis (RMS). After oral dosing, DMF is absorbed from the gastrointestinal tract and rapidly converted by esterases and tricarboxylic acid cycle enzymes into MMF. The pharmacology review of the approval of Tecfidera assumed that “it is the pharmacology of MMF that is most relevant to this application” because MMF was quantifiable and available systemically whereas DMF was not detectable in serum. Therefore, MMF was used for all pharmacokinetic and pharmacodynamic evaluations of DMF in the Tecfidera application, for MMF was assumed to provide the majority, if not all, of the necessary systemic effects leading to the demonstrated clinical efficacy of DMF.

While an exact mechanism of action has not been established, MMF appears to exert its therapeutic effects through activation of the nuclear factor (erythroid-derived 2)-related factor 2 (Nrf2) antioxidant response pathway. The Nrf2 pathway is the primary defense system that cells utilize to respond to a variety of potentially toxic stimuli through upregulation of antioxidant response genes. Preclinical studies collectively indicate that MMF activation of the Nrf2 pathway affects multiple targets and pathways to reduce inflammatory responses in both peripheral and central immune cells and to protect neurons within the central nervous system against inflammatory injury.

1.2. Conclusions on the Substantial Evidence of Effectiveness

As a 505(b)(2) submission, the applicant includes no studies in this NDA to support efficacy and instead the NDA relies entirely on the listed drug, Tecfidera, for evidence of effectiveness. Tecfidera was approved for RMS treatment because patients with RMS who received Tecfidera had a significant reduction in the number and frequency of MS relapses in two adequate, well-controlled studies. With an establishment of bioequivalence of BLS-11 to Tecfidera, the same clinically meaningful effectiveness is assumed for BLS-11.

1.3. Benefit-Risk Assessment

[Benefit-Risk Integrated Assessment](#)

With the approval of Tecfidera (dimethyl fumarate) in 2013 under IND 204063 for the indication of the treatment of relapsing multiple sclerosis, the risks and therapeutic benefits associated with dimethyl fumarate are well known and established. Dimethyl fumarate is rapidly converted to monomethyl fumarate in vivo and monomethyl fumarate is the presumed effector of the clinical effects of systemically administered dimethyl fumarate. The safety profile of monomethyl fumarate, the only known active metabolite of dimethyl fumarate, can be inferred as similar to that of its parent drug, dimethyl fumarate. Although the studies conducted to establish the PK characteristics of monomethyl fumarate in relation to dimethyl fumarate were not designed to establish an extensive safety profile, these PK studies did not raise any specific new clinical safety concerns. Monomethyl fumarate offers different administration attributes and therefore provides an alternative option for the treatment of RMS in adults. Dimethyl fumarate, the parent drug of monomethyl fumarate, is indicated for the treatment of RMS in adults. Given the similarity in safety profile and PK findings, as well as its identity as the sole active metabolite of dimethyl fumarate, monomethyl fumarate merits an approval for the same indication, the treatment of relapsing multiple sclerosis in adults.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Relapsing multiple sclerosis (RMS) is a condition associated with periods of short-term neurological signs and symptoms due to relapses. It is associated with periods of disability due in part to incomplete recovery from relapses. These periods of disability typically last between 3-6 months but commonly resolve thereafter. These features of RMS generally are thought to be due to acute inflammatory events that are disseminated over time and occur in most myelinated areas of the central nervous system and to a lesser extent within the neuropil and even the meninges. However, longer-term irreversible disability may occur independently of	Treatment with dimethyl fumarate results in statistically significant and clinically meaningful reductions in relapses and in occurrences of short-term periods of disability largely unrelated to relapses. This 505(b)(2) application relies entirely on the prior approval of Tecfidera for efficacy assertions because BLS-11, or monomethyl fumarate, is the sole verified biologically active metabolite of the approved product, Tecfidera.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	relapses and represent a distinct but related type of pathophysiology. This application provides evidence from several studies of PK similarities between monomethyl fumarate and its approved parent drug, dimethyl fumarate as the basis for a 505(b)(2) pathway approval.	Monomethyl fumarate is the only systemically detectable active metabolite of dimethyl fumarate and is therefore the presumed effector of dimethyl fumarate's clinical benefits.
Current Treatment Options	There is reasonable certainty that the current approved therapies for RMS are effective in reducing the frequencies of relapses and short-term periods of disability, <i>i.e.</i>, 12 and 24 week confirmed disability. Included amongst these approved therapies is dimethyl fumarate, which is metabolized to the proposed product, monomethyl fumarate.	BLS-11 is bioequivalent to the primary, active metabolite of an approved therapy for RMS, Tecfidera.
Benefit	In patients with RMS, treatment with dimethyl fumarate reduces the frequency of relapses and reduces the proportion of patients with 12-week confirmed disability.	Monomethyl fumarate, as the primary, active metabolite of dimethyl fumarate, is expected to have similar clinical benefit on frequency of relapses and short-term disability prevention as its parent drug, Tecfidera.
Risk and Risk Management	The risks of fumarate preparations are known to include anaphylaxis, angioedema, progressive multifocal leukoencephalopathy, lymphopenia, liver injury, and flushing. These risks can be managed with patient education and clinical awareness with monitoring.	With an establishment of bioequivalence between BLS-11 and Tecfidera, the safety risks of BLS-11 are the same as those noted in the listed drug upon which this application relies, Tecfidera.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
☐	Clinical outcome assessment (COA) data, such as	[e.g., Sec 6.1 Study endpoints]
☐	Patient reported outcome (PRO)	
☐	Observer reported outcome (ObsRO)	
☐	Clinician reported outcome (ClinRO)	
☐	Performance outcome (PerfO)	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
☐	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Sec 2.1 Analysis of Condition]
☐	Observational survey studies designed to capture patient experience data	
☐	Natural history studies	
☐	Patient preference studies (e.g., submitted studies or scientific publications)	
☐	Other: (Please specify)	
☐	Patient experience data that were not submitted in the application, but were considered in this review:	
☐	Input informed from participation in meetings with patient stakeholders	
☐	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
☐	Observational survey studies designed to capture patient experience data	
☐	Other: (Please specify)	
☒	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

Multiple Sclerosis is a chronic disorder of the Central Nervous System (CNS) characterized by recurrent episodes (relapses) of neurologic deficits that are due to one or more areas of acute injury to myelin, oligodendrocytes and to a lesser extent axons and neurons. Areas of acute inflammatory injury may involve subcortical white matter, brainstem, optic nerve, and /or spinal cord. The diagnostic criteria for MS essentially require clinical and/or imaging evidence of a dissemination of these events “in space and time.”¹ Although early relapses may be followed by complete recovery, over time the recurrent relapses are associated with an accumulation of residual deficits and increasing disability.² A slow progression of disability independent of the occurrence of relapses is seen in most patients with MS.^{2,3} This “relapsing and remitting” pattern with or without the slow progression of disability, occurs in approximately 85% of patients with MS. Of those with a typical relapsing onset, approximately one-third will enter a slowly progressive phase with or without superimposed relapses.⁴ Although disability can result from residual deficits following relapses,⁵ relapses are probably not the dominant factor resulting in severe and permanent disability.⁶ Therefore a reduction in the relapse rate does not necessarily correlate with a significant reduction in long-term disability. However, the early frequency and severity of relapses and incomplete recovery from early relapses all tend to predict a more rapid progression of irreversible disability.^{7,8} Relapses are associated with a mean increase of 0.75 on the EDSS scale.⁵ Most of the disability incurred at a relapse improves significantly within two to three months.⁵ Increases on the EDSS that meet generally accepted criteria for confirmed progression of disability for three or six months are usually not sustained beyond one-two years indicating that relapse events are clinically significant but are not the single process driving permanent disability.⁹

2.2. Analysis of Current Treatment Options

The currently approved therapies for RMS are shown in Table 1 below. Available therapies reduce the annualized relapse rate in patients with RMS by 30 to 50%. While a reduction in the number of relapses is desirable, it is unclear whether reducing relapse frequency results in a significant reduction in long-term disability. Differences in methodology and in the populations studied limit interpretation of the full effect of these therapies on permanent disability. Several studies have shown a numeric reduction in some measure of disability that was confirmed 12 and/or 24 weeks after an initial significant increase in a given disability score. However, if a statistically significant reduction was seen in one trial, the result was usually not replicated in a second trial. Although most therapies approved for the treatment of RMS show a reduction in various Magnetic Resonance Imaging (MRI) findings associated with RMS, the interpretation of these neuroimaging changes in the context of patient function do not support the use of any of these MRI measures as primary criteria for the choice of therapy.

Because they were the earliest approved therapies and because there have been few major safety concerns, either a β -interferon or glatiramer acetate are often the initial choice for treatment for new onset typical RMS. Because the interferons share the same presumed mechanism of action and have similar efficacy, if the response is not adequate to one interferon then the choice of next therapy is usually not a different interferon and usually not glatiramer acetate. There are now several approved alternative therapies with efficacy at least comparable to the interferons and glatiramer acetate. The data available are not sufficient to conclude that the efficacy of any of the alternative therapies is superior to the older “first line” therapies.

Each approved therapy has unique benefits and risks. Unless there is strong evidence of superior efficacy and/or a notable lack of safety concerns, any new approved therapy will most likely be used for those who have not responded adequately to the interferons, glatiramer acetate, and possibly one of the approved oral therapies.

Table 1: FDA-approved treatments for Relapsing Forms of Multiple Sclerosis

Approved Drug	Product Name	Relevant Indication	Year Approved	Route & Frequency of Administration	Efficacy Information	Major Safety Concerns	Other Comments
Beta interferon 1b	Betaseron (Betaseron EU)	Relapsing forms of MS	1993	subcutaneous every other day	32% reduction in ARR	None	
Beta interferon 1a	interferon β -1a	Relapsing forms of MS	1996	IM weekly	32% reduction in ARR	hepatotoxicity	
Glatiramer acetate	Copaxone	Relapsing forms of MS	1996	subcutaneous daily	29% reduction in ARR	None	
Mitoxantrone	Novantrone	Relapsing forms of MS	2000	IV every 3 months	60% reduction in ARR 64% reduction in disability	Cardiotoxicity	
Beta interferon 1a	Rebif	Relapsing forms of MS	2002	subcutaneous three times weekly	32% reduction in ARR	hepatotoxicity	
Natalizumab	Tysabri	Relapsing forms of MS	2004	IV every 4 weeks	61% reduction in ARR	Progressive Multifocal Leukoencephalopathy	
Beta interferon 1b	Extavia	Relapsing forms of MS	2009	subcutaneous every other day	30% reduction in ARR	None	

Fingolimod	Gilenya	Relapsing forms of MS	2010	orally once daily	55% reduction in ARR	1 st dose bradycardia, macular edema, impaired pulmonary function tests, fetal risk	indicated for use ≥ 10 years old
Teriflunomide	Aubagio	Relapsing forms of MS	2012	orally once daily	31% reduction in ARR	black box warnings for hepatotoxicity and teratogenicity	
Dimethyl fumarate	Tecfidera	Relapsing forms of MS	2013	orally once daily	49% reduction in ARR	lymphopenia	
PEGylated Interferon Beta	Plegridy	Relapsing forms of MS	2014	subcutaneous every 2 weeks	36% reduction in ARR	None	
Alemtuzumab	Lemtrada	Relapsing forms of MS after inadequate responses to 2 or more other MS treatments	2015	2 courses 12 months apart	49% reduction in ARR	black box warning for serious/fatal autoimmune conditions thrombocytopenia and anti-glomerular basement membrane disease; serious and life-threatening infusion reactions, increased risk of malignancies	not indicated for use in patients less than 18 years of age due to safety concerns
Glatiramer acetate (generic)	various	Relapsing forms of MS	2015	subcutaneous daily	29% reduction in ARR	None	
Ocrelizumab	Ocrevus	Relapsing and Progressive forms of MS	2016	IV every 2 weeks x 2 then IV every 6 months	46% reduction in ARR (RMS) 24% reduction in disability progression (progressive MS)	infusion reactions, increased risk of breast cancer	

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Bafiertam (BLS-11, MMF) currently is not marketed in the United States for any other indication. The United States Food and Drug Administration (FDA) approved Tecfidera (DMF) for

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use in adults with RMS on March 27, 2013. MMF is the primary and only known active metabolite of DMF. The metabolic conversion of DMF into MMF is rapid. Only MMF is detectable in serum. Therefore, the approval of Tecfidera was based on data using MMF as a pharmacokinetic marker.

3.2. Summary of Presubmission/Submission Regulatory Activity

Initial Pre-IND (IND 126454) meeting request: April 29, 2015

Pre-IND meeting written response: June 19, 2015

Original IND submission: April 29, 2016

The submission was made with intention of NDA filing under the 505(b)(2) pathway

IND may proceed letter issued: July 12, 2016

Pre-NDA meeting: September 5, 2017

Pediatric initial study plan approval: September 22, 2017

NDA 210296 submission: January 29, 2018

Filed as a 505(b)(2) pathway standard application.

3.3. Foreign Regulatory Actions and Marketing History

Bafiertam is not approved and is not marketed anywhere in the world for any indication.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Not applicable.

4.2. Product Quality

See the review by the Chemistry, Manufacturing and Control (CMC) reviewers.

4.3. Clinical Microbiology

See the review by the CMC/microbiology reviewers.

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4.4. Nonclinical Pharmacology / Toxicology

See the reviews by the Nonclinical Pharmacology/Toxicology reviewers.

4.5. Clinical Pharmacology

See review by the clinical pharmacology reviewers.

4.6. Devices and Companion Diagnostic Issues

Not applicable.

4.7. Consumer Study Reviews

Not applicable.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

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Table 2: Reviewer Table, All BLS-11 Studies

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
<i>Studies to Support Safety</i>							
BLS-11-101	Phase 1 Single-dose, randomized, open-label, 4-way crossover, pilot study to compare bioavailability of MMF following dosing with BLS-11 and Tecfidera under fasting conditions	- BLS-11 214 mg - BLS-11 200 mg delayed release (DR) capsules - Tecfidera 240 mg DR capsules	PK measures	Single dose	24 (14 male/10 female)	Healthy volunteers	1
BLS-11-102	Phase 1 Single-dose, randomized, open-label, 4-way crossover, pilot study to compare bioavailability of MMF following dosing with BLS-11 and Tecfidera under fasting conditions	- BLS-11 214 mg - BLS-11 200 mg DR capsules - Tecfidera 240 mg DR capsules	PK measures	Single dose	24 (18 male/6 female)	Healthy volunteers	1
BLS-11-103	Phase 1 Single dose, randomized, 2-way, crossover study comparing BLS-11 and Tecfidera To assess bioequivalence of 200 mg BLS-11 and Tecfidera in terms of the Cmax and AUC of MMF after single-dose administration under fasting conditions	- BLS-11 200 mg DR capsules - Tecfidera 240 mg DR capsules	PK measures	Single dose	50 (20 male/30 female)	Healthy volunteers	1
BLS-11-104	Phase 1, Single-dose, randomized, open-label, 2-way crossover study to assess bioequivalence of 190 mg BLS-11 and Tecfidera in terms of the Cmax and AUC of	- BLS-11 190 mg (2 × 95-mg DR capsules) - Tecfidera 240-mg DR capsules	PK measures	Single dose	50 (36 male/14 female)	Healthy volunteers	1

	MMF after single-dose administration under fasting conditions						
BLS-11-105	Phase 1, Single-dose, open-label, randomized, 2-way crossover study to evaluate the effect of food on the bioavailability of MMF	MMF 190 mg (2 × 95-mg DR capsules) with and without food (high-fat meal)	PK measures	Single dose	16 (8 male/8 female)	Healthy volunteers	1
BLS-11-106	Phase 1, Single-dose, open-label, randomized, 2-way crossover study to assess dose proportionality of two doses of MMF	MMF 190 mg (2 × 95-mg DR capsules) with and without food (high-fat meal)	PK measures	Single dose	24 (10 male/14 female)	Healthy volunteers	1
BLS-11-108	Phase 1, Two-dose, open-label, randomized, 2-way crossover study	- MMF 95 mg DR capsule - MMF 190 mg (2 × 95-mg DR capsules)	PK measures	Two doses	16 (9 male/7 female)	Healthy volunteers	

5.2. Review Strategy

This 505(b)(2) NDA submitted on January 29, 2018, supported by pharmacokinetic bridging studies, relies on the listed drug, Tecfidera, for both clinical and nonclinical data. Reference is made to the pre-IND (June 19, 2015) and pre-NDA (September 5, 2017) meeting responses provided the direction for the drug development program and regulatory submission pathway via bridging studies and to the agreement made regarding the content and format of the NDA submission.

5.3. Discussion of Individual Studies/Clinical Trials

Study 1

BLS-11-101 (1980)

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Study Phase

Phase 1

Study Title

A Single-Dose, Randomized, Open-Label, 4-Way Crossover, Pilot Comparative Bioavailability Study of Monomethyl Fumarate 214 mg, 200 mg Delayed-Release Capsules, and Tecfidera 240 mg Delayed-Release Capsules in Healthy Male and Female Volunteers under Fasting Conditions

Study Center

BioPharma Services, 300 Portland St., Suite 100 Columbia, MO, 65201, USA

Study Periods

Period 1: June 04, 2016
Period 2: June 06, 2016
Period 3: June 08, 2016
Period 4: June 10, 2016

Study Objective

The objective of this pilot study is to assess the tolerability, pharmacokinetics, and comparative bioavailability of monomethyl fumarate from three (b) (4) based formulations of Monomethyl Fumarate 214 mg (b) (4) DR capsules, Monomethyl Fumarate 200 mg (b) (4) DR capsules, Monomethyl Fumarate 214 mg (b) (4) DR capsules, and one reference drug, Tecfidera (dimethyl fumarate) delayed-release capsules 240 mg in healthy, non-smoking male and non-pregnant female volunteers under fasting conditions.

Methodology

This study was a single-dose, randomized, open-label, 4-way crossover, comparative bioavailability study of monomethyl fumarate 214 mg and 200 mg delayed-release capsules and Tecfidera 240 mg delayed-release capsules in healthy male and female volunteers under fasting conditions.

Twenty-four (24) healthy, adult male and female subjects between the ages of 19 and 56 years old (inclusive) were enrolled. Screening of subjects occurred within 28 days prior to the study. On Day 1 of Period 1, subjects were randomized to receive one of four possible treatments. Blood for pharmacokinetic (PK) evaluation of the treatment was collected at the times specified in the protocol until twenty-four hours post-dose. In each period, subjects were confined from

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at least ten hours prior to dosing until at least twenty-four hours post-dose. The washout period was at least two days between treatments. The applicant performed a post-study follow-up after at least seven days of last dose to assess for AEs.

Number of Subjects (Planned and Analyzed)

A total of twenty-four subjects enrolled in the study, and twenty-four subjects completed the study. All twenty-four subjects enrolled in the study were included in the study population PK and safety findings.

Demographics

A total of twenty-four subjects were enrolled in the study. All twenty-four subjects received each of the four treatments and completed the study. Mean ($\pm$ standard deviation [SD]) age of subjects was 38 years ($\pm$ 11), with a range of 19 to 56 years. The majority of subjects were male (58%, 14/24 subjects); and all subjects were black (83%, 20/24 subjects) or white (17%, 4/24 subjects). Mean ($\pm$ SD) body mass index (BMI) was 26.6 kg/m² ($\pm$ 2.6), with a range of 18.9 to 29.8 kg/m².

Diagnosis and Main Criteria for Inclusion

All subjects enrolled in this study were judged by the PI to be normal, healthy volunteers who met all inclusion criteria and met no exclusion criteria.

Study Treatment(s)

Table 3: Applicant Table, Treatments for Study BLS-11-101

Treatment Code	T1 (Test)	T2 (Test)	T3 (Test)	R (Reference)
Drug Name:	Monomethyl Fumarate	Monomethyl Fumarate	Monomethyl Fumarate	TECFIDERA [®] (dimethyl fumarate)
Strength:	214 mg	200 mg	214 mg	240 mg
Dosage Form:	(b) (4) DR Capsules	(b) (4) DR Capsules	(b) (4) DR Capsules	Delayed-release Capsules
Manufactured by/for:	Banner Life Sciences; BLS	Banner Life Sciences; BLS	Banner Life Sciences; BLS	Biogen, Inc.
Dose:	1 x 214 mg	1 x 200 mg	1 x 214 mg	1 x 240 mg

Duration of Treatment

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Subjects will be confined to the clinic from at least 10 hours prior to dosing until at least 24-hours post-dose in Period 4, for a total of at least 178 hours (for approximately 8 days) in the study.

Reference Product, Dose, Duration, Mode of Administration, and Batch Number

Tecfidera, 240 mg delayed-release capsule, one dose, oral, Lot Number: R12058

Criteria for Evaluation

Pharmacokinetics: Serial blood samples were obtained for the determination of each treatment's PK parameters in plasma, including C_{max} , T_{max} , AUC_t , AUC_{inf} , λ , and $t_{1/2}$. Pharmacokinetic parameters were calculated using non-compartmental analysis (NCA) method using SAS Version 9.4.

Safety: Safety endpoints included all AEs, physical examinations, vital signs (heart rate, blood pressure, and temperature), 12-lead electrocardiograms (ECG), and clinical laboratory tests (hematology, serum chemistry, infectious serology, and urinalysis.)

Statistical Methods

Pharmacokinetics: Descriptive statistics (min, max, median, mean, standard deviation, and coefficient of variability) of all pharmacokinetic parameters were provided for the test and reference products. ANOVA including sequence, subjects nested within sequence, period, and treatment was performed on the ln-transformed data for AUC_t , AUC_{inf} , and C_{max} , and on the un-transformed data for T_{max} , λ , and $T_{1/2}$. T_{max} was analyzed using an additional non-parametric test (Wilcoxon test). The 90% confidence intervals (CI) of the Test/Reference ratios of geometric least-squares means for AUC_t , AUC_{inf} , and C_{max} were calculated by exponentiating the difference in least square means (LSMEANS) and associated 90% confidence interval estimates from the ANOVA.

Safety: All clinical safety and tolerability data were listed by subject. Safety data including all AEs, ECGs, vital signs, and clinical laboratory evaluations were summarized descriptively by treatment and time point of collection. AEs were coded with the Medical Dictionary for Regulatory Activities (MedDRA).

Results

PK Results

Per the applicant's CSR for study 1980:

"This fasted pilot study showed that:

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- Test treatment T1 demonstrated a much lower rate and extent of bioavailability of monomethyl fumarate compared to the reference treatment based on the Geometric Least-Squares Mean (GLSM) ratios and associated 90% confidence intervals for the Test/Reference ratios of C_{max} (for rate) and AUC_{inf} and AUC_t (for extent).
- Test treatment T2 demonstrated a much lower rate and extent of bioavailability of monomethyl fumarate compared to the reference treatment based on the GLSM ratios and associated 90% confidence intervals for the Test/Reference ratios of C_{max} , AUC_{inf} , and AUC_t .
- Test treatment T3 demonstrated comparable extent of bioavailability based on the GLSM ratios and associated 90% confidence intervals for the Test/Reference ratios of AUC_{inf} and AUC_t . However, Test Product T3 showed higher rate of bioavailability than the Reference product as shown by the Test/Reference GLSM ratio and associated 90% confidence interval for C_{max} .”

“This pilot study shows that the test treatment T3 demonstrated the closest comparable bioavailability to the reference product among all three test formulations.”

“Intra-subject variability was calculated to be 23.48% for AUC_t , 22.51% for AUC_{inf} and 33.44% for C_{max} for MMF under fasting conditions.”

Safety Results

There were no deaths during the conduct of this study.

No serious AEs were reported during the conduct of this study.

There were 73 adverse events involving 12 subjects in this study.

There were 10 AEs associated with three subjects who received Treatment T1, which consisted of (in MedDRA Preferred Terminology (PT)):

Flushing	8
Neck pain	1
Pruritus	1

There were 10 AEs associated with six subjects who received Treatment T2, which consisted of (in MedDRA Preferred Terminology (PT)):

Flushing	5
Pruritus	1
Nausea	1
Dizziness	1
Abdominal pain	1

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There were 35 AEs associated with 10 subjects who received Treatment T3, which consisted of (in MedDRA Preferred Terminology (PT)):

Flushing	32
Abdominal pain upper	1
Nausea	1
Vomiting	1

There were 18 AEs associated with seven subjects who received Treatment R, which consisted of (in MedDRA Preferred Terminology (PT)):

Flushing	16
Diarrhea	1
Abdominal pain	1

No AEs associated with clinical laboratory tests were experienced by the subjects at post-study.

Study 2

BLS-11-102 (1981)

Study Phase

Phase 1

Study Title

A Single-Dose, Randomized, Open-Label, 4-Way Crossover, Pilot Comparative Bioavailability Study of Monomethyl Fumarate 214 mg and 200 mg Delayed-Release Capsules and Tecfidera 240 mg Delayed-Release Capsules in Healthy Male and Female Volunteers under Fasting Conditions

Study Center

BioPharma Services, 300 Portland St., Suite 100 Columbia, MO, 65201, USA

Study Periods

Period 1: June 24, 2016
Period 2: June 26, 2016
Period 3: June 28, 2016

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Period 4: June 30, 2016

Study Objectives

The objective of this pilot study was to assess the tolerability, pharmacokinetics and comparative bioavailability of monomethyl fumarate from three (b) (4) formulations of monomethyl fumarate 214 mg (b) (4) DR capsules, Monomethyl Fumarate 200 mg (b) (4) DR capsules, and Monomethyl Fumarate 214 mg (b) (4) DR capsules, and one reference drug, Tecfidera (dimethyl fumarate) delayed-release capsules 240 mg, in healthy male and female volunteers under fasting conditions.

Methodology

This was a single-dose, randomized, open-label, 4-way crossover, 4-sequence, pilot comparative bioavailability study of MMF 214-mg and 200-mg DR capsules and Tecfidera 240-mg DR capsules. The study was conducted at a single study center. The objective of this pilot study was to assess the tolerability, pharmacokinetics, and comparative bioavailability of MMF from 3 (b) (4) formulations of MMF: MMF 214-mg (b) (4) DR capsules, MMF 200-mg (b) (4) DR capsules, MMF 214-mg (b) (4) DR capsules, and Tecfidera (DDF) 240-mg DR capsules as a reference drug, administered to 24 healthy nonsmoking males and females. Female subjects could not be pregnant. Subjects were administered an oral dose of 1 × 214-mg ((b) (4) and (b) (4) or 1 × 200-mg ((b) (4) or 1 × 240-mg (Tecfidera) DR capsule under fasting conditions. Safety assessments included AEs/SAEs, clinical laboratory evaluations, and vital signs/physical examination findings.

Number of Subjects (Planned and Analyzed)

A total of twenty-four subjects were enrolled in the study. All 24 subjects received each of the four treatments and completed the study.

Demographics

The majority of subjects were male (75%, 18/24 subjects); and all subjects were black (71%, 17/24 subjects) or white (25%, 6/24 subjects). Mean ($\pm$ SD) age of subjects was 36 years ($\pm$ 12), with a range of 21 to 56 years. Mean ($\pm$ SD) BMI was 26.3 kg/m² ($\pm$ 3.1), with a range of 19.3 to 29.9 kg/m².

Diagnosis and Main Criteria for Inclusion

All subjects enrolled in this study were judged by the PI to be normal, healthy volunteers who met all inclusion criteria and met no exclusion criteria.

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Study Treatments

MMF 214-mg	(b) (4)	DR capsules
MMF 200-mg	(b) (4)	DR capsules
MMF 214-mg	(b) (4)	DR capsules
Tecfidera (DDF) 240-mg		DR capsules

Duration of Treatment

Subjects will be confined to the clinic from at least 10 hours prior to dosing until at least 24-hours post-dose in Period 4, for a total of at least 178 hours (for approximately 8 days) in the study.

Reference Product, Dose, Duration, Mode of Administration, and Batch Number

Tecfidera, 240 mg delayed release capsule, one dose, oral, Lot Number: R12058

Criteria for Evaluation

Pharmacokinetics: Serial blood samples were obtained for the determination of each treatment's PK parameters in plasma, including C_{max} , T_{max} , AUC_t , AUC_{inf} , λ , and $t_{1/2}$. Pharmacokinetic parameters were calculated using non-compartmental analysis (NCA) method using SAS Version 9.4.

Safety: Safety endpoints included all AEs, physical examinations, vital signs (heart rate, blood pressure, and temperature), 12-lead electrocardiograms (ECG), and clinical laboratory tests (hematology, serum chemistry, infectious serology, and urinalysis.)

Statistical Methods

Pharmacokinetic: Descriptive statistics (min, max, median, mean, standard deviation, and coefficient of variability) of all pharmacokinetic parameters were provided for the test and reference products. ANOVA including sequence, subjects nested within sequence, period, and treatment was performed on the ln-transformed data for AUC_t , AUC_{inf} , and C_{max} , and on the un-transformed data for T_{max} , λ , and $T_{1/2}$. T_{max} was analyzed using an additional non-parametric test (Wilcoxon test). The 90% confidence intervals (CI) of the Test/Reference ratios of geometric least squares means for AUC_t , AUC_{inf} and C_{max} were calculated based on the least square means (LSMEANS) and ESTIMATE of the ANOVA.

Safety: All clinical safety and tolerability data were listed by subject. Safety data including all AEs, ECGs, vital signs, and clinical laboratory evaluations were summarized descriptively by

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treatment and time point of collection. AEs were coded with the Medical Dictionary for Regulatory Activities (MedDRA).

Results

PK Results

Per the CSR for Study 1981:

“This fasted pilot study showed that

- Test Treatment T4 had comparable extent of bioavailability to the reference treatment as shown by the AUC_{inf} T/R GLSMR (geometric least-squares mean ratio) of 98.87% with a corresponding 90% CI of 92.44 - 105.74%, but a lower rate of bioavailability than that of the reference treatment as shown by the C_{max} T/R GLSMR of 83.90%, and a corresponding 90% CI of 70.26 - 100.19%.
- Test treatment T5 demonstrated lower extent of bioavailability compared to the reference treatment with a T/R GLSMR for In-transformed AUC_t of 85.75% and a corresponding 90% CI of 79.89 - 92.03%. The T/R GLSMR for In-transformed AUC_{inf} was 90.58% and a corresponding 90% CI of 84.61 - 96.98%. In addition, the test treatment T5 also demonstrated a much lower rate of bioavailability compared to the reference treatment with an In-transformed C_{max} T/R GLSMR of 66.94% and a corresponding 90% CI of 56.06 - 79.94%.
- Test treatment T6 demonstrated comparable extent of bioavailability to the reference treatment as shown by the AUC_t T/R GLSMR of 100.59% with a corresponding 90% CI of 93.62 - 108.07%. The T/R GLSMR for In-transformed AUC_{inf} was 102.02% and a corresponding 90% CI of 95.65 - 108.82%. Furthermore, the test treatment T6 demonstrated slightly lower rate of bioavailability compared to the reference treatment with an In-transformed C_{max} T/R GLSMR of 89.79%, and a corresponding 90% CI of 74.99 - 107.51%.
- Formulation T6 demonstrated the closest comparable bioavailability to the reference product from all three test formulations.
- The ISCV for AUC_t , AUC_{inf} , and C_{max} in this study were 14.37%, 12.09%, and 37.05% respectively.

The non-parametric analysis of T_{max} for monomethyl fumarate under fasting conditions detected a significant difference in T_{max} between T6 and the reference treatment product. There was no significant difference in T_{max} detected between T4, T5, and the reference treatment product [Wilcoxon two-sample test, two-sided normal (Z) approximation].”

Safety Results

There were no deaths reported during the conduct of this study.

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There were no serious AEs reported during the conduct of this study.

There were 100 adverse events involving 15 subjects in this study.

There were 28 AEs associated with five subjects who received Treatment T4, which consisted of (in MedDRA Preferred Terminology (PT)):

Flushing	16
Burning sensation	5
Pruritus	5
Diarrhea	1
Nausea	1

There were 12 AEs associated with four subjects who received Treatment T5, which consisted of (in MedDRA Preferred Terminology (PT)):

Flushing	6
Pruritus	4
Nausea	1
Diarrhea	1

There were 32 AEs associated with 10 subjects who received Treatment T6, which consisted of (in MedDRA Preferred Terminology (PT)):

Flushing	29
Nausea	1
Vomiting	1
Vessel puncture site pain	1

There were 28 AEs associated with 11 subjects who received Treatment R, which consisted of (in MedDRA Preferred Terminology (PT)):

Flushing	20
Pruritus	5
Chest discomfort	1
Headache	1
Nausea	1

No AEs associated with clinical laboratory tests were noted by the subjects at post-study follow-up.

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There was one instance of vomiting and two instances of diarrhea during the conduct of this study.

Subject (b) (6) experienced the AE vomiting 2.85 hours after dosing with Treatment T6 in Period 2. The subject was permitted to continue with the study.

Subject (b) (6) experienced the AE diarrhea 17.90 hours after dosing with Treatment T4 in Period 2. The subject was permitted to continue with the study.

Subject (b) (6) experienced the AE diarrhea 11.23 hours after dosing with Treatment T5 in Period 1. The subject was permitted to continue with the study.

Study 3

BLS-11-103

Study Phase

Phase 1

Study Title

A Single-Dose, Randomized, Open-Label, 2-Way Crossover, Comparative Bioavailability Study of BLS-11 (Monomethyl Fumarate) 200 mg Delayed-Release Capsules and Tecfidera (Dimethyl Fumarate) 240 mg Delayed-Release Capsules in Healthy Male and Female Subjects under Fasting Conditions

Study Center

Celerion, 2420 West Baseline Road, Tempe, Arizona 85283, USA

Study Period

Date of first enrollment: December 26, 2016

Date of last completed: February 16, 2017

Study Objectives

Primary:

- To determine the pharmacokinetic (PK) profiles of monomethyl fumarate (MMF) after a single oral dose of the test product, BLS-11 200 mg delayed-release capsule, and the reference

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product, Tecfidera 240 mg dimethyl fumarate (DMF) delayed-release capsule, in healthy male and non-pregnant female subjects under fasting conditions.

- To assess if the test and reference products (indicated above) were bioequivalent (BE) in terms of the C_{max} and AUC values of MMF after single-dose administration under fasting conditions.

Secondary:

- To evaluate the safety and tolerability of a single dose of BLS-11 200 mg delayed-release capsule and a single oral dose of Tecfidera 240 mg DMF delayed-release capsule in healthy male and non-pregnant female subjects under fasting conditions.

Methodology

This was a single-dose, randomized, open-label, 2-way crossover study evaluating the comparative PK of the test product versus the reference product under fasting conditions.

Fifty healthy, adult male and non-pregnant female subjects were enrolled. Space constraints at the clinical research unit (CRU) may have required subjects to be divided into 2 dosing groups of approximately equal size for dosing, as needed.

Screening of subjects occurred within 21 days prior to the first dose.

Subjects were randomized to one of two treatment sequences prior to the first dose.

In each period, subjects received a single oral dose of BLS-11 200 mg delayed-release capsule (Test product) or Tecfidera 240 mg DMF delayed-release capsule (Reference product), followed by blood sampling (including pre-dose sample) up to 24 hours post-dose for the determination of plasma concentrations of MMF.

There was a washout period of at least 2 days between the two doses.

Safety was monitored throughout the study by repeated clinical and laboratory evaluations.

Subjects were housed on Day -1 of Period 1, at the time indicated by the CRU, until after the 24-hour blood draws and/or study procedures in Period 2. At all times, a subject may have been required to remain at the CRU for longer at the discretion of the Principal Investigator (PI) or designee.

The clinic attempted to contact all subjects (including subjects who terminated the study early) using their standard procedures approximately 7 days after the last study drug administration to determine if any adverse events (AEs) had occurred since the last study visit.

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Number of Subjects (Planned and Analyzed)

A total of fifty-six subjects were enrolled in the study, and 50 subjects completed the study. There were fifty subjects included in PK analyses.

Demographics

According to the CSR for Study BLS-11-103:

Table 4: Applicant Table, Demographics of Study BLS-11-103

Trait	Category/Statistics	Randomized Treatment Sequence		Overall
		AB	BA	
Gender	Female	14 (56%)	16 (64%)	30 (60%)
	Male	11 (44%)	9 (36%)	20 (40%)
Race	Asian	1 (4%)	0 (0%)	1 (2%)
	Black or African American	1 (4%)	2 (8%)	3 (6%)
	White	23 (92%)	21 (84%)	44 (88%)
	White, American Indian/Alaska Native	0 (0%)	1 (4%)	1 (2%)
	White, Black or African American	0 (0%)	1 (4%)	1 (2%)
Ethnicity	Hispanic or Latino	16 (64%)	19 (76%)	35 (70%)
	Not Hispanic or Latino	9 (36%)	6 (24%)	15 (30%)

		Randomized Treatment Sequence		
Trait	Category/Statistics	AB	BA	Overall
Age* (yrs)	n	25	25	50
	Mean	39.5	37.6	38.5
	SD	10.52	9.79	10.10
	Minimum	19	21	19
	Median	41.0	41.0	41.0
	Maximum	55	51	55
Weight (kg)	n	25	25	50
	Mean	70.99	71.25	71.12
	SD	10.951	10.745	10.738
	Minimum	50.6	51.1	50.6
	Median	71.70	70.30	71.00
	Maximum	93.6	95.9	95.9
Height (cm)	n	25	25	50
	Mean	166.0	164.4	165.2
	SD	9.74	11.64	10.66
	Minimum	147	146	146
	Median	166.0	162.0	165.0
	Maximum	188	186	188
BMI (kg/m ²)	n	25	25	50
	Mean	25.656	26.305	25.981
	SD	2.5352	2.5913	2.5582
	Minimum	19.10	21.86	19.10
	Median	25.360	27.180	26.260
	Maximum	29.50	29.52	29.52
Treatment A: A single oral dose of BLS-11 200 mg MMF Treatment B: A single oral dose of Tecfidera® 240 mg DMF Age is calculated at the date of informed consent. BMI = Body mass index				

Source: CSR Study BLS-11-103, Table 11-1, pages 35-36

Diagnosis and Main Criteria for Inclusion

All subjects enrolled in this study were judged by the Investigator to be normal, healthy volunteers who met all inclusion and none of the exclusion criteria or were approved by the applicant.

Study Treatment(s)

Treatment A: a single oral dose of 200 mg MMF (1 x 200 mg delayed-release capsule; Lot No. 14700842MB) at Hour 0 on Day 1, with 240 mL of water.

Treatment B: a single oral dose of Tecfidera 240 mg DMF (1 x 240 mg delayed release capsule; Lot No. R12058) at Hour 0 on Day 1, with 240 mL of water.

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Duration of Treatment

Healthy volunteers were housed on Day -1 of Period 1, at the time indicated by the CRU, until after the 24-hour blood draw and/or study procedures in Period 2. There was a washout period of 2 days between the two doses.

Reference Product, Dose, Duration, Mode of Administration, and Batch Number

Tecfidera (DMF), 240 mg delayed release capsule, once, oral, Lot No. R12058. Subjects received a single oral dose at Hour 0 on Day 1, with 240 mL of water.

Criteria for Evaluation

Pharmacokinetics: Serial blood samples for measurement of MMF plasma concentrations were collected immediately (within 15 minutes) prior to dosing, and then at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 9, 10, 11, 12, and 24 hours post-dose, in each period. The plasma concentration-time data for MMF were analyzed using non-compartmental methods. The plasma PK parameters of interest following a single dose of BLS-11 200 mg MMF and Tecfidera 240 mg DMF included AUC_{0-t} , AUC_{0-inf} , $AUC_{\%extrap}$, C_{max} , t_{max} , k_{el} , and $t_{1/2}$.

Safety: Safety was evaluated by clinical laboratory tests, physical examination, vital signs, 12-lead electrocardiograms (ECGs), and AEs.

Statistical Methods

Pharmacokinetics: Plasma concentrations were listed by subject with sample time and summarized by treatment. Plasma PK parameters were listed by subject and summarized by treatment using descriptive statistics. Mean and individual plasma concentration versus time profiles were presented on linear and semi-log scales. Linear mean plots were presented with and without standard deviation (SD). An analysis of variance (ANOVA) was performed on the natural log (ln)-transformed AUC_{0-t} , AUC_{0-inf} , and C_{max} using SAS PROC MIXED. The ANOVA model included sequence, treatment, and period as fixed effects, and subject nested within sequence as a random effect. Each ANOVA included calculation of least-squares means (LSM) of the ln-transformed parameter as well as the LSM difference between treatments.

Safety: All reported AEs were coded with the Medical Dictionary for Regulatory Activities (MedDRA) Version 19.1. All AEs were listed by subject, including verbatim term, coded term, severity, and relationship to study drug. AEs were tabulated by System Organ Class (SOC) and Preferred Term. In addition, Gastrointestinal (GI) tolerability, defined as all AEs pertaining to nausea, vomiting, diarrhea, and abdominal pain were tabulated both as individual terms and as combined GI tolerability. All concomitant medications recorded during the study were coded

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with the World Health Organization (WHO) Drug Dictionary Version 01 Sep 2016 and listed.

Descriptive statistics (n, mean, SD, median, minimum, and maximum) were reported for numeric clinical laboratory results by time point. Change from baseline at each time point was calculated using the previous clinical assessment made for each subject. In addition, a shift table describing out-of-normal range shifts was provided for clinical laboratory results. Out-of-normal range and clinically significant laboratory values were listed by subject. All laboratory results were listed in by-subject data listings. Summary statistics (n, mean, SD, minimum, median, and maximum) were reported for vital sign measurements and change from baseline by treatment for each time point. All vital sign results were listed in a by-subject data listing. All ECG results were listed in a by-subject data listing.

Results

Pharmacokinetic Results

Per the applicant: "Following administration of a single oral dose of BLS-11 200 mg MMF, a slight delay in the rise of MMF concentration was observed when compared to DMF. Plasma MMF remained BLQ in the majority of subjects until at least 2 hours post-dose, with C_{max} of MMF achieved at 4 hours post-dose. Conversely, following a single oral dose of Tecfidera 240 mg DMF, plasma MMF concentrations were measurable in the majority of the subjects at 1-hour post-dose, with C_{max} of MMF achieved at 2.6 hours post-dose. The plasma concentrations of MMF for > 50% of subjects fell to BLQ again starting at 7 and 6.5 hours post-dose for [MMF] and [DMF], respectively.

"The mean figures above indicated the mean peak plasma concentrations of MMF were attained at 4.5 hours post-dose for [MMF] and at 2.5 hours post-dose for [DMF].

"The mean AUC and C_{max} values were somewhat higher following a single oral dose of BLS-11 200 mg MMF compared to Tecfidera 240 mg DMF. It was noted that there was inter-subject variability in the PK parameter estimates, as indicated by the CV% (24% to 48%) and G_{eom} CV% (25% to 47%) for the 3 exposure-based parameters. Median t_{max} value occurred about 1.5 hours later following BLS-11 (4.00 hours) when compared to Tecfidera (2.56 hours). Because of the delayed-release formulation of both treatments, the minimum and maximum t_{max} values were quite variable, spanned over the range of 2.00 to 6.50 hours post-dose for Treatment A, and between 1.00 to 9.01 hours post-dose for Treatment B. The mean $t_{1/2}$ values were similar for both treatments, at approximately 0.50 hours following administration of BLS-11 and Tecfidera.

"The mean $AUC_{\%extrap}$ values were less than 1% for both treatments, suggesting the MMF concentration-time profiles were well characterized.

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“The statistical analysis results showed that only AUC_{0-t} and AUC_{0-inf} values met the acceptance criteria for bioequivalence between [MMF] and [DMF], but not C_{max} .”

Reviewer Comment: The failure of BLS-11 to achieve bioequivalence criteria for C_{max} in this study is unlikely to be clinically significant. The mechanism of action of BLS-11 requires long-term maintenance at steady state level. A steady state level would require chronic daily administration for months. Therefore, BLS-11 failing to achieve C_{max} as quickly as DMF following a single dose is unlikely to alter the efficacy of BLS-11 when it is administered on a chronic basis.

Safety Results

There were no deaths, serious adverse events (SAEs), or subject discontinuations due to AEs in this study. A total of fifty-eight treatment-emergent AEs (TEAEs) were reported by 33 (66%) subjects following BLS-11 200 mg MMF, and 46 AEs were reported by 29 (58%) subjects following Tecfidera 200 mg DMF. The most common AE was flushing, experienced by 25 (50%) subjects each following MMF and DMF. Overall, ninety-six AEs were mild in severity, and eight were moderate in severity. There were no remarkable findings in the safety assessments for AEs, vital signs, ECGs, clinical laboratory, or physical examinations.

The most frequently reported AE during this study was mild flushing, experienced 25 times by 25 (50%) subjects each following BLS-11 200 mg MMF and Tecfidera 200 mg DMF. AE onset was between 34 minutes and 20 hours; total duration was 13 minutes to 17 hours after onset, with the majority of instances lasting approximately 1 - 3 hours duration. The PI considered all flushing AEs to be likely related to the study drug. While the incidence of GI tolerability event was lower in the BLS-11 200 mg MMF (10%) versus the Tecfidera (14%), the low number of events because of the single dose nature of the study does not allow for a meaningful comparison.

All remaining AEs were reported by four or fewer subjects each ($\leq 8\%$).

Table 5: Applicant Table, Adverse Events, Study BLS-11-103

Adverse Events*	Treatment	
	A	B
Number of Subjects Dosed	50 (100%)	50 (100%)
Number of Subjects With TEAEs	33 (66%)	29 (58%)
Number of Subjects Without TEAEs	17 (34%)	21 (42%)
Eye disorders	1 (2%)	0 (0%)
Eye irritation	1 (2%)	0 (0%)
Gastrointestinal disorders	5 (10%)	7 (14%)
Abdominal discomfort	0 (0%)	1 (2%)
Abdominal distension	1 (2%)	1 (2%)
Abdominal pain	0 (0%)	1 (2%)
Abdominal pain lower	1 (2%)	0 (0%)

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Abdominal pain upper	2 (4%)	1 (2%)
Abdominal tenderness	1 (2%)	0 (0%)
Diarrhea	0 (0%)	2 (4%)
Dyspepsia	0 (0%)	1 (2%)
Flatulence	0 (0%)	1 (2%)
Nausea	1 (2%)	3 (6%)
Gastrointestinal tolerability†	5 (10%)	7 (14%)
Abdominal pain	4 (8%)	3 (6%)
Abdominal discomfort	0 (0%)	1 (2%)
Abdominal distension	1 (2%)	1 (2%)
Abdominal pain	0 (0%)	1 (2%)
Abdominal pain lower	1 (2%)	0 (0%)
Abdominal pain upper	2 (4%)	1 (2%)
Abdominal tenderness	1 (2%)	0 (0%)
Suprapubic pain	1 (2%)	0 (0%)
Nausea	1 (2%)	3 (6%)
Nausea	1 (2%)	3 (6%)
Diarrhea	0 (0%)	3 (6%)
Diarrhea	0 (0%)	2 (4%)
Flatulence	0 (0%)	1 (2%)
General disorders and administration site conditions	6 (12%)	2 (4%)
Feeling hot	1 (2%)	0 (0%)
Suprapubic pain	1 (2%)	0 (0%)
Vessel puncture site hemorrhage	0 (0%)	2 (4%)
Vessel puncture site induration	1 (2%)	0 (0%)
Vessel puncture site pain	3 (6%)	2 (4%)
Vessel puncture site swelling	2 (4%)	0 (0%)
Musculoskeletal and connective tissue disorders	1 (2%)	1 (2%)
Arthralgia	1 (2%)	0 (0%)
Muscle spasms	0 (0%)	1 (2%)
Nervous system disorders	9 (18%)	2 (4%)
Dizziness	1 (2%)	0 (0%)
Headache	4 (8%)	2 (4%)
Presyncope	2 (4%)	0 (0%)
Somnolence	1 (2%)	0 (0%)
Tremor	1 (2%)	0 (0%)
Skin and subcutaneous tissue disorders	2 (4%)	2 (4%)
Pruritus	2 (4%)	2 (4%)
Rash macular	1 (2%)	0 (0%)
Rash papular	1 (2%)	0 (0%)
Vascular disorders	25 (50%)	25 (50%)
Flushing	25 (50%)	25 (50%)
*Adverse events are classified according to MedDRA® Version 19.1 †Defined as all AEs pertaining to abdominal pain (abdominal pain, abdominal pain lower, abdominal pain upper abdominal tenderness, abdominal distension, abdominal discomfort and suprapubic pain), nausea, vomiting, and diarrhea (diarrhea and flatulence). Treatment A: A single oral dose of BLS-11 200 mg MMF Treatment B: A single oral dose of Tecfidera® 240 mg DMF		

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Source: CSR, Study BLS-11-103, Table 12-1, pages 44-45

All AEs resolved without sequelae.

Study 4
BLS-11-104

Study Phase

Phase 1

Study Title

A Single-Dose, Randomized, Open-Label, 2-Way Crossover, Comparative Bioavailability Study of BLS-11 (Monomethyl Fumarate) 190 mg Administered as Two 95 mg Delayed-Release Capsules and Tecfidera (Dimethyl Fumarate) 240 mg Delayed-Release Capsules in Healthy Male and Female Subjects under Fasting Conditions

Study Center

Celerion, 2420 West Baseline Road, Tempe, Arizona 85283, USA

Study Period

Date of first enrollment: January 6, 2017
Date of last completed: February 16, 2017

Study Objectives

Primary:

- To determine the PK profiles of MMF after a single oral dose of the test product, BLS-11 190 mg administered as two 95 mg delayed-release capsules, and the reference product, Tecfidera 240 mg DMF delayed-release capsule, in healthy male and non-pregnant female subjects under fasting conditions.
- To assess if the test and reference products (indicated above) were bioequivalent in terms of the C_{max} and AUC values of MMF after single-dose administration under fasting conditions.

Secondary:

- To evaluate the safety and tolerability of a single dose of BLS-11 190 mg administered as two 95 mg delayed-release capsules and a single oral dose of Tecfidera 240 mg DMF delayed-release capsule in healthy male and non-pregnant female subjects under fasting conditions.

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Methodology

This was a single-dose, randomized, open-label, 2-way crossover study evaluating the comparative pharmacokinetics (PK) of the test product versus the reference product under fasting conditions.

Fifty healthy, adult male and non-pregnant female subjects were enrolled. Space constraints at the clinical research unit (CRU) required subjects to be divided into 2 dosing groups of approximately equal size for dosing, as needed. Screening of subjects occurred within 21 days prior to the first dose. Subjects were randomized to one of two treatment sequences prior to the first dose. In each period, subjects received a single oral dose of BLS-11 190 mg administered as two 95 mg delayed-release capsules (test product) or Tecfidera 240 mg DMF delayed-release capsule (reference product), followed by blood sampling (including pre-dose samples) up to 24 hours post-dose for the determination of plasma concentrations of MMF. There was a washout period of at least 2 days between the two doses. Safety was monitored throughout the study by repeated clinical and laboratory evaluations. Discontinued subjects were not replaced. Subjects were housed on Day -1 of Period 1, at the time indicated by the CRU, until after the 24-hour blood draw and/or study procedures in Period 2. At all times, a subject may have been required to remain at the CRU for longer at the discretion of the PI or designee. The clinic attempted to contact all subjects (including subjects who terminated the study early) using their standard procedures approximately 7 days after the last study drug administration to determine if any AEs had occurred since the last study visit.

Number of Subjects (Planned and Analyzed)

A total of fifty-six subjects were enrolled in the study, and 49 subjects completed the study. There were fifty subjects included in PK and safety analyses.

Demographics

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Table 6: Applicant Table, Demographics, Study BLS-11-104

Trait	Category/Statistics	Randomized Treatment Sequence		Overall
		AB	BA	
Gender	Female	6 (24%)	8 (32%)	14 (28%)
	Male	19 (76%)	17 (68%)	36 (72%)
Race	Black or African American	6 (24%)	4 (16%)	10 (20%)
	White	19 (76%)	19 (76%)	38 (76%)
	White, Black or African American	0 (0%)	2 (8%)	2 (4%)
Ethnicity	Hispanic or Latino	15 (60%)	12 (48%)	27 (54%)
	Not Hispanic or Latino	10 (40%)	13 (52%)	23 (46%)
Age* (yrs)	n	25	25	50
	Mean	34.4	38.0	36.2
	SD	9.85	8.22	9.17
	Minimum	21	26	21
	Median	35.0	37.0	35.5
	Maximum	50	55	55
Weight (kg)	n	25	25	50
	Mean	72.98	74.78	73.88
	SD	9.450	12.512	11.011
	Minimum	54.6	46.4	46.4
	Median	72.50	76.00	73.55
	Maximum	100.6	100.1	100.6
Height (cm)	n	25	25	50
	Mean	168.6	170.3	169.5
	SD	7.55	10.58	9.14
	Minimum	154	151	151
	Median	170.0	170.0	170.0
	Maximum	185	198	198
BMI (kg/m ²)	n	25	25	50
	Mean	25.625	25.678	25.651
	SD	2.4142	2.9237	2.6537
	Minimum	20.17	19.80	19.80
	Median	25.650	25.620	25.635
	Maximum	29.62	29.47	29.62
Treatment A: A single oral dose of BLS-11 190 mg (2 x 95 mg) MMF Treatment B: A single oral dose of Tecfidera® 240 mg (1 x 240 mg) DMF * Age is calculated at the date of informed consent. BMI = Body mass index The category 'White, Black or African-American' represents subjects who selected both racial categories 'White' and 'Black or African-American' on the CRF.				

Diagnosis and Main Criteria for Inclusion

All subjects enrolled in this study were judged by the Investigator to be normal, healthy volunteers who met all inclusion and none of the exclusion criteria or were approved by the applicant.

Study Treatment

Treatment A: BLS-11 (MMF). Subjects were administered a single oral dose of 190 mg

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MMF (2 × 95 mg delayed-release capsule; Lot No.: 14700847MA) at Hour 0 on Day 1, with 240 mL of water.

Treatment B: Subjects were administered a single oral dose of Tecfidera 240 mg DMF (1 × 240 mg delayed-release capsule; Lot No. R12058) at Hour 0 on Day 1, with 240 mL of water.

Duration of Treatment

Subjects were housed on Day -1 of Period 1, at the time indicated by the CRU, until after the 24-hour blood draw and/or study procedures in Period 2. There was a washout period of 2 days between the two doses.

Reference Product, Dose, Duration, Mode of Administration, and Batch Number

The reference product was Tecfidera. Subjects were administered a single oral dose of Tecfidera 240 mg DMF (1 × 240 mg delayed-release capsule; Lot No. R12058) at Hour 0 on Day 1, with 240 mL of water.

Criteria for Evaluation

Pharmacokinetics: Serial blood samples for measurement of MMF plasma concentrations were collected immediately (within 15 minutes) prior to dosing, and then at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 9, 10, 11, 12, and 24 hours post-dose, in each period. The plasma concentration-time data for MMF was analyzed using non-compartmental methods. The plasma PK parameters of interest following a single dose of BLS-11 190 mg (2 × 95 mg) MMF and Tecfidera 240 mg DMF included AUC_{0-t} , AUC_{0-inf} , $AUC_{\%extrap}$, C_{max} , t_{max} , K_{el} , and $t_{1/2}$.

Safety: Safety was evaluated by clinical laboratory tests, physical examination, vital signs, 12-lead electrocardiograms (ECGs), and adverse events (AEs).

Statistical Methods

Pharmacokinetics: Plasma concentrations were listed by subject and sample time and summarized by treatment, and plasma PK parameters were listed by subject and summarized by treatment using descriptive statistics. Mean and individual plasma concentration versus time profiles were presented on linear and semi-log scales. Linear mean plots were presented with and without SD. An analysis of variance (ANOVA) was performed on the natural log (ln)-transformed AUC_{0-t} , AUC_{0-inf} , and C_{max} using SAS PROC MIXED. The ANOVA model included sequence, treatment, and period as fixed-effects, and subject nested within sequence as a random-effect. Each ANOVA included calculation of least-squares means (LSM) of the ln-transformed parameter as well as the LSM difference between treatments.

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Bafiertam (monomethyl fumarate)

Safety: All reported AEs were coded with the Medical Dictionary for Regulatory Activities (MedDRA) Version 19.1. All AEs were listed by subject, including verbatim term, coded term, severity, and relationship to study drug. AEs were tabulated by SOC and Preferred Term. All concomitant medications recorded during the study were coded with the World Health Organization (WHO) Drug Dictionary Version 01 Sep 2016 and listed. Descriptive statistics (n, mean, SD, median, minimum, and maximum) were reported for numeric clinical laboratory results by treatment and time point. Change from baseline at each time point was calculated using the previous clinical assessment made for each subject. In addition, a shift table describing out-of-normal range shifts was provided for clinical laboratory results. Out-of-normal range and clinically significant laboratory values were listed by subject. All laboratory results were listed in by-subject data listings. Summary statistics (n, mean, SD, minimum, median, and maximum) were reported for vital sign measurements and change from baseline by treatment for each time point. All vital sign results were listed in by-subject data listing. All ECG results were listed in by-subject data listing.

Results

Pharmacokinetic Results: From the plasma MMF concentration versus time profiles, a delay in the rise of MMF concentration was evident for both treatments consistent with the formulation design. For MMF, plasma MMF remained BLQ for > 50% of subjects until 2 hours post-dose, with mean peak plasma concentration of MMF achieved about 4.5 hours after dosing. Conversely, for DMF, BLQ values were observed in > 50% of subjects only until 0.5 hour post-dose and the peak plasma MMF concentration was attained at approximately 2.5 hours post-dose. The plasma concentrations of MMF fell to BLQ for > 50% of subjects again after 7.5 and 7 hours post-dose for MMF and DMF, respectively.

The applicant noted that there was reasonable variability within the PK parameter estimates, as indicated by the CV% (24% to 33%) and G_{eom} CV% (24% to 35%) for the 3 exposure-based PK parameters. The median t_{max} value occurred 1.53 hours later following BLS 11 administration (4.03 hours) when compared to Tecfidera (2.50 hours). The mean $t_{1/2}$ value was approximately 0.60 hours for MMF and DMF. The mean $AUC_{\%extrap}$ values were approximately 1.3% for both treatments, suggesting the MMF concentration-time profiles were characterized adequately.

The statistical comparisons of PK parameters of plasma MMF, AUC_{0-t} , AUC_{0-inf} , and C_{max} following a single oral dose of BLS-11 190 mg (2 × 95 mg) MMF versus a single oral dose of Tecfidera 240 mg (1 × 240 mg) DMF resulted in 90% CIs entirely within the 80.00% – 125.00% reference interval. These findings demonstrate that a single oral dose of BLS-11 190 mg (2 × 95 mg) is bioequivalent to Tecfidera 240 mg DMF (1 × 240 mg).

Reviewer Comment: Please refer to the Agency's PK review for further discussion and details regarding the PK findings of bioequivalence.

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Safety Results: There were no deaths, SAEs, or subject discontinuations due to AEs in this study. One patient discontinued the study after receiving a dose of BLS-11 for reasons unrelated to the study, (personal reasons, quoted as a “family emergency”) and therefore data regarding Tecfidera are only available in 49 patients. A total of forty-two TEAEs were reported by 31 (62%) subjects following BLS-11 190 mg MMF, and 37 AEs were reported by 29 (59%) subjects following Tecfidera 240 mg DMF.

The most common AE was flushing, experienced by 30 (60%) subjects following MMF and 25 (51%) subjects following DMF.

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Table 7: Applicant Table, Adverse Events, Study BLS-11-104

Adverse Events*	Treatment	
	A	B
Number of Subjects Dosed	50 (100%)	49 (100%)
Number of Subjects With TE Adverse Events	31 (62%)	29 (59%)
Number of Subjects Without TE Adverse Events	19 (38%)	20 (41%)
Gastrointestinal tolerability #	1 (2%)	2 (4%)
Abdominal pain (pooled)	1 (2%)	1 (2%)
Diarrhoea	0 (0%)	2 (4%)
Nausea	0 (0%)	1 (2%)
Cardiac disorders	1 (2%)	0 (0%)
Palpitations	1 (2%)	0 (0%)
Gastrointestinal disorders	1 (2%)	2 (4%)
Abdominal distension	0 (0%)	1 (2%)
Abdominal pain	1 (2%)	0 (0%)
Abdominal pain upper	0 (0%)	1 (2%)
Diarrhoea	0 (0%)	2 (4%)
Nausea	0 (0%)	1 (2%)
General disorders and administration site conditions	2 (4%)	1 (2%)
Chills	1 (2%)	0 (0%)
Feeling hot	1 (2%)	0 (0%)
Vessel puncture site erythema	0 (0%)	1 (2%)
Vessel puncture site pain	0 (0%)	1 (2%)
Vessel puncture site swelling	0 (0%)	1 (2%)
Nervous system disorders	1 (2%)	0 (0%)
Dizziness	1 (2%)	0 (0%)
Hypoaesthesia	1 (2%)	0 (0%)
Psychiatric disorders	1 (2%)	0 (0%)
Anxiety	1 (2%)	0 (0%)
Euphoric mood	1 (2%)	0 (0%)
Reproductive system and breast disorders	1 (2%)	0 (0%)
Metrorrhagia	1 (2%)	0 (0%)
Respiratory, thoracic and mediastinal disorders	1 (2%)	2 (4%)
Nasal congestion	0 (0%)	2 (4%)
Rhinorrhoea	1 (2%)	0 (0%)
Skin and subcutaneous tissue disorders	2 (4%)	1 (2%)
Pruritus generalised	1 (2%)	0 (0%)
Skin fissures	1 (2%)	1 (2%)
Vascular disorders	30 (60%)	25 (51%)
Flushing	30 (60%)	25 (51%)

Treatment A: A single oral dose of BLS-11 190 mg (2 x 95 mg) MMF
Treatment B: A single oral dose of Tecfidera® 240 mg (1 x 240 mg) DMF
*Adverse events are classified according to MedDRA® Version 19.1
Defined as all adverse events pertaining to abdominal pain (abdominal pain, abdominal pain upper, abdominal distension), nausea, vomiting and diarrhea.
TE = Treatment-emergent

Source: CSR Study BLS-11-104, Table 12-1, page 45

All AEs were mild in severity and resolved spontaneously at the end of study. There were no additional noteworthy findings in the safety assessments for AEs, vital signs, ECGs, clinical laboratory, or physical examinations.

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The safety and tolerability profile of BLS-11 at 190 mg was similar to that of Tecfidera 240 mg.

Reviewer Comment: Flushing is a common AE with DMF. The safety findings after a single dose of MMF appear consistent with safety data from single doses of DMF.

Study 5

BLS-11-105

Study Phase

Phase 1

Study Title

A Single-Dose, Open-Label, Randomized, 2-Way Crossover Study to Determine the Effect of Food on the Relative Bioavailability of BLS-11 (Monomethyl Fumarate) 190 mg Delayed-Release Capsules in Healthy Male and Female Subjects

Study Center

Celerion, 2420 West Baseline Road, Tempe, Arizona 85283, USA

Study Period

Date of first enrollment: February 18, 2017

Date of last completed: April 6, 2017

Study Objectives

Primary:

- To evaluate the effect of food (a high-fat meal) on the bioavailability of MMF after a single oral dose of BLS-11 190 mg administered as two 95 mg delayed-release capsules in healthy subjects.

Secondary:

- To evaluate the safety and tolerability of a single dose of BLS-11 190 mg administered as two 95 mg delayed-release capsules in healthy male and non-pregnant female subjects under fed and fasting conditions.

Methodology

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This was a single-dose, open-label, randomized, 2-way crossover study evaluating the bioavailability of MMF after a single oral dose of BLS-11 190 mg administered as two 95 mg delayed-release capsules administered under fed conditions (Test Regimen) versus under fasting conditions (Reference Regimen). Sixteen (16) healthy, adult male and non-pregnant female subjects were enrolled. Screening of subjects occurred within 21 days prior to the first dose. Subjects were randomized to one of two treatment sequences prior to the first dose. Each subject received both the Test and Reference regimens over two dose periods in a randomized crossover fashion. Blood samples were collected from pre-dose to 24 hours post-dose of each regimen for the determination of plasma concentrations of MMF. There was a washout period of 4 days between the two doses. Safety was monitored throughout the study by repeated clinical and laboratory evaluations. Discontinued subjects were not replaced. Subjects were housed on Day -1 of Period 1, at the time indicated by the clinical research unit (CRU), until after the 24-hour blood draw and/or study procedures in Period 2. At all times, a subject may have been required to remain at the CRU for longer at the discretion of the PI or designee. The clinic attempted to contact all subjects (including subjects who terminated the study early) using their standard procedures approximately 7 days after the last study drug administration to determine if any adverse events (AEs) had occurred since the last study visit.

Number of Subjects (Planned and Analyzed)

A total of sixteen subjects were enrolled in the study, and sixteen subjects completed the study. There were 16 subjects included in the pharmacokinetic (PK) and safety analyses.

Demographics

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Table 8: Applicant Table, Demographics, Study BLS-11-105

Trait	Category/Statistics	Randomized Treatment Sequence		Overall
		AB	BA	
Gender	Female	5 (63%)	3 (38%)	8 (50%)
	Male	3 (38%)	5 (63%)	8 (50%)
Race	Asian	0 (0%)	1 (13%)	1 (6%)
	Native Hawaiian/Pacific Islander	2 (25%)	0 (0%)	2 (13%)
	White	6 (75%)	7 (88%)	13 (81%)
Ethnicity	Hispanic or Latino	7 (88%)	7 (88%)	14 (88%)
	Not Hispanic or Latino	1 (13%)	1 (13%)	2 (13%)
Age* (yrs)	n	8	8	16
	Mean	31.6	35.4	33.5
	SD	9.32	8.30	8.74
	Minimum	21	20	20
	Median	31.0	35.0	34.5
	Maximum	44	46	46
Weight (kg)	n	8	8	16
	Mean	70.84	72.64	71.74
	SD	10.520	10.459	10.176
	Minimum	51.3	58.9	51.3
	Median	72.10	70.20	70.20
	Maximum	85.6	88.4	88.4
Height (cm)	n	8	8	16
	Mean	164.0	166.9	165.4
	SD	7.03	7.75	7.30
	Minimum	156	156	156
	Median	162.5	171.5	167.5
	Maximum	174	174	174
BMI (kg/m ²)	n	8	8	16
	Mean	26.251	25.934	26.093
	SD	3.0698	2.3797	2.6585
	Minimum	21.04	22.92	21.04
	Median	27.630	25.515	26.595
	Maximum	29.26	29.10	29.26

Treatment A: A single oral dose of BLS-11 190 mg MMF Under Fed Conditions
Treatment B: A single oral dose of BLS-11 190 mg MMF Under Fasted Conditions
* Age is calculated at the date of informed consent.
BMI = Body mass index

Source: CSR, Study BLS-11-105, Table 11-1, page 34

Diagnosis and Main Criteria for Inclusion

All subjects enrolled in this study were judged by the Investigator to be normal, healthy volunteers who met all inclusion and none of the exclusion criteria or were approved by the applicant.

Study Treatments

Treatment A: BLS-11 (MMF), administered as a single oral dose of BLS-11 190 mg MMF (2 × 95 mg) delayed-release capsules (Lot No. 14700847MA), with 240 mL of water, under fed conditions (high-fat meal).

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Treatment B: BLS-11 (MMF), administered as a single oral dose of BLS-11 190 mg MMF (2 × 95 mg) delayed-release capsules (Lot No. 14700847MA), with 240 mL of water, under fasted conditions.

Duration of Treatment

Subjects were housed on Day -1 of Period 1, at the time indicated by the CRU, until after the 24-hour blood draws and/or study procedures in Period 2. There was a washout period of 4 days between the two doses.

Reference Product, Dose, Duration, Mode of Administration, and Batch Number

The reference product was BLS-11 (MMF), administered as a single oral dose of BLS-11 190 mg MMF (2 × 95 mg) delayed-release capsules (Lot No. 14700847MA), with 240 mL of water, under fasted conditions.

Criteria for Evaluation

Pharmacokinetics: Serial blood samples for measurement of MMF plasma concentrations were collected immediately (within 15 minutes) prior to dosing and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 9, 10, 11, 12, and 24 hours post-dose in each period. The plasma concentration-time data for MMF was analyzed using non-compartmental methods. The plasma PK parameters of interest following a single dose of BLS-11 190 mg (2 × 95 mg) MMF under fed and fasting conditions included: AUC_{0-t}, AUC_{0-inf}, AUC_{%extrap}, C_{max}, t_{max}, K_{el}, t_{lag}, and t_{1/2}.

Safety: Safety was evaluated by clinical laboratory tests, physical examination, vital signs, 12-lead electrocardiograms (ECGs), and AEs.

Statistical Methods:

Pharmacokinetics: Plasma concentrations were listed by subject and sample time and summarized by treatment, and plasma PK parameters were listed by subject and summarized by treatment using descriptive statistics. Mean and individual plasma concentration versus time profiles were presented on linear and semi-log scales. Linear mean plots were presented with and without standard deviation (SD). An analysis of variance (ANOVA) was performed on the natural log (ln)-transformed AUC_{0-t}, AUC_{0-inf}, and C_{max} using SAS PROC MIXED. The ANOVA model included sequence, treatment, and period as fixed effects, and subject nested within sequence as a random effect. Each ANOVA included calculation of least-squares means (LSM) of the ln-transformed parameter as well as the LSM difference between treatments.

Safety: All reported AEs were coded with the Medical Dictionary for Regulatory Activities (MedDRA) Version 19.1. All AEs were listed by subject, including verbatim term, coded term,

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severity, and relationship to study drug. AEs were tabulated by SOC and Preferred Term. All concomitant medications recorded during the study were coded with the World Health Organization (WHO) Drug Dictionary Version 01 Sep 2016 and listed. Descriptive statistics (n, mean, SD, median, minimum, and maximum) were reported for numeric clinical laboratory results by treatment and time point. Change from baseline at each time point was calculated using the previous clinical assessment made for each subject. In addition, a shift table describing out-of-normal range shifts was provided for clinical laboratory results. Out-of-normal range and clinically significant laboratory values were listed by subject. All laboratory results were listed in by-subject data listings. Summary statistics (n, mean, SD, minimum, median, and maximum) were reported for vital sign measurements and change from baseline by treatment for each time point. All vital sign results were listed in a by-subject data listing. All ECG results were listed in a by-subject data listing.

Results

Pharmacokinetic Results: Following administration of a single oral dose of BLS-11 190 mg MMF under fed conditions, there was an apparent delay in the rise of MMF concentration where the peak plasma MMF concentration was attained after 9 hours post-dose. Plasma MMF remained BLQ in > 50% of the subjects until 7 hours post-dose. Conversely, following administration of BLS-11 190 mg MMF under fasting conditions, the majority (> 50%) of the subjects had measurable plasma MMF concentrations by 3 hours post-dose. The plasma concentrations of MMF in > 50% of subjects fell to BLQ again starting at 12 and 7.5 hours post-dose for BLS-11 190 mg MMF under fed conditions and BLS-11 190 mg MMF under fasted conditions, respectively. In 2 subjects, there were no quantifiable plasma MMF concentrations throughout the 12-hour period following 190 mg MMF under fed conditions; there was no sampling between 12 and 24 hours post-dose.

The AUCs and C_{max} values were lower following a single oral dose of BLS-11 190 mg MMF under fed conditions compared to the same dosage under fasting conditions. There was also greater overall variability reported amongst the plasma MMF PK parameters in 190 mg MMF under fed conditions than in 190 mg MMF under fasted conditions. The mean $AUC_{\%extrap}$ value for 190 mg MMF under fed conditions was 2.3% and 0.9% for 190 mg MMF under fasted conditions, thus indicating that the exposure profiles for both treatments were adequately characterized.

Median t_{max} occurred 3.25 hours later following BLS-11 190 mg MMF (4.00 hours) administration under fed conditions compared to fasting conditions (7.25 hours). Because of the delayed-release formulation, the minimum and maximum t_{max} values spanned over a wide range, 3 to 10 hours for 190 mg MMF under fed conditions and 3 to 6 hours for 190 mg MMF under fasted conditions and with median t_{lag} for 190 mg MMF under fed conditions of 6.25 hours and 2.50 hours post-dose for 190 mg MMF under fasted conditions. The variation in t_{max} for 190 mg MMF under fed conditions contributed to the multiphasic appearance of the above

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mean plasma MMF concentration versus time plots. The mean $t_{1/2}$ values for both treatments were comparable, at 0.56 hours and 0.48 hours under fed and fasting conditions, respectively.

The results of the applicant's statistical analysis showed that AUC_{0-t} and C_{max} of MMF following a single oral dose of BLS-11 190 mg MMF under fed conditions were apparently approximately 25% and 36%, respectively, lower than that after administration under fasting conditions. However, it is possible that this is the result of delayed gastric emptying due to the high-fat meal, and the lack of plasma sampling between 12 and 24 hours post-dose is likely to have missed a significant part of the AUC.

The applicant concluded that "[a] high-fat meal appears to have delayed the absorption and decreased the plasma exposure to MMF following administration of a single dose of BLS-11 190 mg. Because of the lack of sampling between 12 and 24 hours post-dose under fed condition, the extent of the food effect cannot be accurately assessed."

Reviewer Comment: Please refer to the Agency's PK review for further details and additional conclusions.

Safety Results: There were no deaths, serious adverse events (SAEs), or subject discontinuations due to AEs in this study.

Overall, a total of twenty-five mild treatment-emergent AEs (TEAEs) were reported by 13 (81%) subjects, with 10 (63%) subjects following a single oral dose of BLS-11 190 mg MMF under fed conditions and nine (56%) subjects following a single oral dose of BLS-11 190 mg MMF under fasting conditions.

The most common AE was flushing, experienced by 13 (81%) subjects between both treatments.

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Table 9: Applicant Table, Adverse Events, Study BLS-11-105

Adverse Events*	Treatment		Overall
	A	B	
Number of Subjects Dosed	16 (100%)	16 (100%)	16 (100%)
Number of Subjects With TE Adverse Events	10 (63%)	9 (56%)	13 (81%)
Number of Subjects Without TE Adverse Events	6 (38%)	7 (44%)	3 (19%)
Gastrointestinal tolerability #	2 (13%)	1 (6%)	3 (19%)
Abdominal discomfort	1 (6%)	0 (0%)	1 (6%)
Constipation	1 (6%)	0 (0%)	1 (6%)
Diarrhoea	0 (0%)	1 (6%)	1 (6%)
Ear and labyrinth disorders	1 (6%)	0 (0%)	1 (6%)
Tinnitus	1 (6%)	0 (0%)	1 (6%)
Gastrointestinal disorders	2 (13%)	1 (6%)	3 (19%)
Abdominal discomfort	1 (6%)	0 (0%)	1 (6%)
Constipation	1 (6%)	0 (0%)	1 (6%)
Diarrhoea	0 (0%)	1 (6%)	1 (6%)
Injury, poisoning and procedural complications	0 (0%)	1 (6%)	1 (6%)
Procedural anxiety	0 (0%)	1 (6%)	1 (6%)
Nervous system disorders	1 (6%)	0 (0%)	1 (6%)
Headache	1 (6%)	0 (0%)	1 (6%)
Vascular disorders	10 (63%)	9 (56%)	13 (81%)
Flushing	10 (63%)	9 (56%)	13 (81%)
Treatment A: A single oral dose of BLS-11 190 mg MMF Under Fed Conditions			
Treatment B: A single oral dose of BLS-11 190 mg MMF Under Fasted Conditions			
*Adverse events are classified according to MedDRA® Version 19.1			
# Defined as all adverse events pertaining to abdominal pain, such as abdominal discomfort, and all AEs pertaining to nausea, vomiting, constipation, and diarrhea.			
TE = Treatment-emergent			

Source: CSR, Study BLS-11-105, Table 12-1, page 42

There were no remarkable findings in the safety assessments for AEs, vital signs, ECGs, clinical laboratory, or physical examinations.

The applicant concluded, “[a] single oral dose of BLS-11 190 mg MMF, administered under fed and fasting conditions, appeared to be safe and well tolerated for the healthy adult subjects in this study.”

Reviewer Comment: There were no new safety issues identified in this study.

Study 6

BLS-11-106

Study Phase

Phase 1

Study Title

CDER Clinical Review Template

Version date: September 6, 2017 for all NDAs and BLAs

Clinical Review
Paul Lee, M.D., Ph.D.
NDA-210296
Bafiertam (monomethyl fumarate)

A Single-Dose, Open-Label, Randomized, Two Way Crossover Study to Determine the Effect of Food (High Fat Meal) on the Relative Bioavailability of BLS-11 (Monomethyl Fumarate) 95 mg Delayed- Release Capsules in Healthy Male and Female Subjects

Study Center

Celerion, 2420 West Baseline Road, Tempe, Arizona 85283, USA

Study Period

Date of first enrollment: May 31, 2017

Date of last completed: August 3, 2017

Study Objectives

Primary:

- To evaluate the effect of food (a high-fat meal) on the bioavailability of MMF after a single oral dose of BLS-11 190 mg administered as two 95 mg delayed-release capsules in healthy subjects.

Secondary:

- To evaluate the safety and tolerability of a single dose of BLS-11 190 mg administered as two 95 mg delayed-release capsules in healthy male and non-pregnant female subjects under fed and fasting conditions.

Methodology

This was a single-dose, open-label, randomized, 2-way crossover study evaluating the relative bioavailability of MMF after a single oral dose of BLS-11 190 mg administered as two 95 mg delayed-release capsules under fed conditions (Test Regimen) versus under fasting conditions (Reference Regimen). Twenty-four (24) adult male and non-pregnant female, healthy, non-smoking subjects were enrolled. Subjects were randomized to one of two treatment sequences prior to the first dose. Each subject received both the Test and Reference regimens over two dose periods in a randomized crossover fashion. Blood samples for the determination of plasma concentrations of MMF were collected from pre-dose to 12 hours post-dose, or pre-dose to 24 hours post-dose of the fasted or fed treatments, respectively. There was a washout period of at least 5 days between the two doses. Safety was monitored throughout the study by repeated clinical and laboratory evaluations. The clinic attempted to contact all subjects (including subjects who terminated the study early) using their standard procedures approximately 7 days after the last study drug administration to determine if any adverse events (AEs) had occurred since the last study visit.

Number of Subjects (Planned and Analyzed)

Twenty-four subjects were enrolled in the study, and twenty-one subjects completed the study. The reasons why three subjects failed to complete the study are as follows:

- One subject discontinued due to an adverse event.
- One subject did not return for the second treatment condition.
- One patient was failed to follow-up after completing the treatments.

There were 22 subjects included in pharmacokinetic (PK) analyses and 24 subjects included in safety analyses.

Demographics

Table 10: Applicant Table: Demographics, Study BLS-11-106

Trait	Category/Statistics	Randomized Treatment Sequence		Overall
		AB	BA	
Sex	Female	7 (58%)	7 (58%)	14 (58%)
	Male	5 (42%)	5 (42%)	10 (42%)
Race	Asian	1 (8%)	0 (0%)	1 (4%)
	Black or African American	0 (0%)	1 (8%)	1 (4%)
	White	11 (92%)	11 (92%)	22 (92%)
Ethnicity	Hispanic or Latino	8 (67%)	6 (50%)	14 (58%)
	Not Hispanic or Latino	4 (33%)	6 (50%)	10 (42%)
Age* (yrs)	n	12	12	24
	Mean	35.0	35.1	35.0
	SD	11.31	8.13	9.63
	Minimum	20	22	20
	Median	34.0	36.5	36.0
	Maximum	52	50	52
Weight (kg)	n	12	12	24
	Mean	68.22	69.63	68.93
	SD	8.544	14.543	11.687
	Minimum	55.8	46.9	46.9
	Median	67.60	66.25	66.80
	Maximum	85.3	94.8	94.8
Height (cm)	n	12	12	24
	Mean	164.7	165.4	165.0
	SD	10.25	9.80	9.81
	Minimum	150	152	150
	Median	163.0	167.0	164.0
	Maximum	189	184	189
BMI (kg/m ²)	n	12	12	24
	Mean	25.277	25.205	25.241

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Trait	Category/Statistics	Randomized Treatment Sequence		Overall
		AB	BA	
	SD	2.9498	3.2348	3.0278
	Minimum	18.72	19.91	18.72
	Median	25.445	25.950	25.950
	Maximum	29.01	29.83	29.83
Treatment A: A single oral dose of BLS-11 190 mg MMF Under Fed Conditions				
Treatment B: A single oral dose of BLS-11 190 mg MMF Under Fasting Conditions				
*Age is calculated at the date of informed consent.				
BMI = Body mass index				

Source: CSR, Study BLS-11-106, Table 11-1, pages 34-35

Diagnosis and Main Criteria for Inclusion

All subjects enrolled in this study were judged by the Principal Investigator (PI) to be normal, healthy volunteers who met all inclusion and none of the exclusion criteria.

Study Treatments

Treatment A: BLS-11 (MMF), administered as a single oral dose of BLS-11 190 mg MMF (2 × 95 mg) delayed-release capsules (Lot No. 14700847MA), with 240 mL of water, under fed conditions (high-fat meal).

Treatment B: BLS-11 (MMF), administered as a single oral dose of BLS-11 190 mg MMF (2 × 95 mg) delayed-release capsules (Lot No. 14700847MA), with 240 mL of water under fasted conditions.

Duration of Treatment

Subjects were housed on Day -1 of Period 1, at the time indicated by the clinical research unit (CRU), until after the 24-hour blood draw and/or study procedures. A subject may have been required to remain at the CRU for longer at the discretion of the PI or designee. Duration of confinement was at least 10.5 hours prior to dosing until at least 12 hours following the last blood draw in each study period, for a total of at least 34.5 (Fasted) or 46.5 hours (Fed).

Reference Product, Dose, Duration, Mode of Administration, and Batch Number

The reference product was BLS-11 (MMF), administered as a single oral dose of BLS-11 190 mg MMF (2 × 95 mg) delayed-release capsules (Lot No. 14700847MA), with 240 mL of water under fasted conditions.

Criteria for Evaluation

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Pharmacokinetics: Serial blood samples for measurement of MMF plasma concentrations were collected over a 24- hour period (please note that different sampling schedules were followed for the fed and fasted treatment conditions: The plasma concentration-time data for MMF was analyzed using non-compartmental methods. The plasma PK parameters of interest following a single dose of BLS-11 190 mg (2 x 95 mg) MMF under fed and fasting conditions included AUC_{0-t} , AUC_{0-inf} , $AUC_{\%extrap}$, C_{max} , t_{max} , K_{el} , t_{lag} , and $t_{1/2}$.

Safety: Safety was evaluated by clinical laboratory tests, physical examination, vital signs, 12-lead electrocardiograms (ECGs), and AEs.

Statistical Methods

Pharmacokinetics: Plasma concentrations were listed by subject and sample time and summarized by treatment, and plasma PK parameters were listed by subject and summarized by treatment using descriptive statistics. Mean and individual plasma concentration versus time profiles were presented on linear and semi-log scales. Linear mean plots were presented with and without standard deviation (SD). An analysis of variance (ANOVA) was performed on the natural log (ln)-transformed AUC_{0-t} , AUC_{0-inf} , and C_{max} using SAS PROC MIXED. The ANOVA model included sequence, treatment, and period as fixed effects, and subject nested within sequence as a random effect. Each ANOVA included calculation of least-squares means (LSM) of the ln-transformed parameter as well as the LSM difference between treatments.

Safety: No inferential statistics were performed for safety assessments.

Results

Pharmacokinetic Results: Following administration of a single oral dose of BLS-11 190 mg MMF under fed conditions, there was an apparent delay in the rise of MMF concentration whereby the peak plasma MMF concentration was attained at approximately 6.5 hours post-dose. Conversely, following administration of BLS-11 190 mg MMF under fasting conditions, C_{max} was achieved at approximately 3.5 hours post-dose. Additionally, it appeared the overall exposure of MMF in the plasma was lower when a single oral dose of 190 mg BLS-11 was administered under fed conditions. However, the above figures of the mean MFF concentration versus time profiles following 190 mg BLS-11 under fed conditions are not representative of the individual subject profiles owing to the fact that peak plasma MMF concentrations occurred at different times over a wide range (from 3 to 24 hours post-dose) in individual subjects following a single oral dose of 190 mg BLS-11 under fed conditions.

The mean C_{max} value (all subjects) was lower following a single oral dose of BLS-11 190 mg MMF under fed conditions compared to the same dosage under fasting conditions. However, mean AUC_{0-t} and AUC_{0-inf} values were similar between both treatments. The mean $AUC_{\%extrap}$

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was < 2% for both treatment conditions; suggestive of adequately characterized exposure profiles for both treatments as well.

Median t_{max} occurred 6.75 hours later following BLS-11 190 mg MMF administration under fed conditions (10.75 hours) compared to fasting conditions (4.00 hours). Because of the delayed-release formulation of BLS-11 in combination with a high-fat meal, the minimum and maximum t_{max} values in individual subjects spanned over a large range of 3.00 to 24.00 hours for treatment under fed conditions with median t_{lag} of 6.25 hours and median t_{last} of 16.00 hours post-dose. For treatment under fasted conditions, t_{max} was found to range from 2.5 to 5.51 hours with median t_{lag} of 0.00 hours and median t_{last} of 7.03 hours post-dose. The large variation in t_{max} for Treatment A in individual subjects contributed to the appearance of multiple peaks in the mean plasma MMF concentration versus time profiles. The mean $t_{1/2}$ values for both treatments were comparable, at approximately 0.53 hours and 0.55 hours under fed and fasting conditions, respectively.

The applicant concluded, “[t]he results of the statistical analysis showed that mean AUC_{0-t} and AUC_{0-inf} values of plasma MMF following a single oral dose of BLS-11 190 mg MMF administered under fed conditions only differed by < 5% when compared to administration under fasting conditions. However, mean C_{max} was approximately 20% lower under the fed conditions compared to the fasting conditions.”

Reviewer Comment: Please refer to the Agency’s PK review for further details and discussion of the study’s conclusions.

Safety Results

There were no deaths or serious adverse events (SAEs) in this study.

One subject was discontinued from the study due to the AE of vomiting (see Section 8.4.3).

Overall, AEs were experienced by 75% of subjects, with 16 (70%) subjects following BLS-11 190 mg MMF Fed and 13 (57%) subjects following BLS-11 190 mg MMF Fasted.

The most common AE reported by both groups was flushing. All AEs were mild in severity.

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Table 11: Applicant Table, Adverse Events, Study BLS-11-106

Adverse Events*	Treatment		Overall
	BLS-11 Fed	BLS-11 Fasted	
Number of Subjects Dosed	23 (100%)	23 (100%)	24 (100%)
Number of Subjects With TE Adverse Events	16 (70%)	13 (57%)	18 (75%)
Number of Subjects Without TE Adverse Events	7 (30%)	10 (44%)	6 (25%)
Gastrointestinal tolerability†	3 (13%)	1 (4%)	3 (13%)
Abdominal pain (pooled)	2 (9%)	1 (4%)	2 (8%)
Constipation	1 (4%)	0 (0%)	1 (4%)
Nausea	1 (4%)	0 (0%)	1 (4%)
Vomiting	1 (4%)	0 (0%)	1 (4%)
Nausea + vomiting	1 (4%)	0 (0%)	1 (4%)
Gastrointestinal disorders	3 (13%)	1 (4%)	3 (13%)
Abdominal discomfort	0 (0%)	1 (4%)	1 (4%)
Abdominal distension	1 (4%)	0 (0%)	1 (4%)
Abdominal pain upper	1 (4%)	0 (0%)	1 (4%)
Constipation	1 (4%)	0 (0%)	1 (4%)
Nausea	1 (4%)	0 (0%)	1 (4%)
Vomiting	1 (4%)	0 (0%)	1 (4%)
General disorders and administration site conditions	5 (22%)	2 (9%)	7 (29%)
Catheter site oedema	0 (0%)	1 (4%)	1 (4%)
Catheter site pain	0 (0%)	1 (4%)	1 (4%)
Chills	0 (0%)	1 (4%)	1 (4%)
Feeling hot	3 (13%)	0 (0%)	3 (13%)
Infusion site pain	1 (4%)	0 (0%)	1 (4%)
Vessel puncture site haemorrhage	1 (4%)	0 (0%)	1 (4%)
Nervous system disorders	3 (13%)	0 (0%)	3 (13%)
Headache	2 (9%)	0 (0%)	2 (8%)
Paraesthesia	1 (4%)	0 (0%)	1 (4%)
Skin and subcutaneous tissue disorders	3 (13%)	1 (4%)	4 (17%)
Erythema	1 (4%)	0 (0%)	1 (4%)
Pruritus	0 (0%)	1 (4%)	1 (4%)
Pruritus generalised	2 (9%)	0 (0%)	2 (8%)
Vascular disorders	12 (52%)	12 (52%)	15 (63%)
Flushing	12 (52%)	12 (52%)	15 (63%)

*Adverse events are classified according to MedDRA® Version 19.1
BLS-11 Fed: A single oral dose of BLS-11 190 mg MMF Under Fed Conditions
BLS-11 Fasted: A single oral dose of BLS-11 190 mg MMF Under Fasting Conditions
†Defined as all AEs pertaining to abdominal pain, such as abdominal pain upper, abdominal discomfort, abdominal distension, and all AEs pertaining to nausea, vomiting, constipation and diarrhea.
TE = Treatment-emergent

Source: CSR, Study BLS-11-106, Table 12-1, page 42

There were no remarkable findings in the safety assessments for AEs, vital signs, ECGs, clinical laboratory, or physical examinations.

The applicant concluded, “[a] single oral dose of BLS-11 190 mg MMF, administered under fed and fasting conditions, appeared to be safe and well tolerated for the healthy adult subjects in this study.”

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Reviewer Comment: No new safety issues were identified in Study BLS-11-106. The patient discontinuation due to vomiting is discussed in Section 8.4.3.

Study 7

Study BLS-11-108

Study Phase

Phase 1

Study Title

A Single-Dose, Open-Label, Randomized, 2-Way Crossover Study Evaluating the Pharmacokinetics of 1x95 mg Monomethyl Fumarate Delayed-Release Capsule and 2x95 mg Delayed-Released Capsules in Healthy Male and Female Subjects under Fasting Conditions

Study Center

BioPharma Services USA Inc., 300 Portland St., Suite 100, Columbia, MO., 65201

Study Period

Period 1: October 31, 2017

Period 2: November 03, 2017

Study Objectives

The objective of this study was to assess the pharmacokinetics and dose proportionality of monomethyl fumarate following single-dose administration of 1 x 95 mg and 2 x 95 mg Monomethyl Fumarate 95 mg Delayed Release Capsules in healthy male and female subjects under fasting conditions.

Pharmacokinetics and dose proportionality of monomethyl fumarate were to be determined based on the results of the comparative bioavailability analysis.

Methodology

This was a single-dose, open-label, randomized, two-period, two-sequence, two-treatment, two-way crossover pharmacokinetic study of monomethyl fumarate, administered as 1 x 95 mg and 2 x 95 mg Monomethyl Fumarate 95 mg Delayed Release Capsules to healthy, non-smoking (at least for 6 months prior to first study drug administration) male and non-pregnant female

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volunteers under fasting conditions. Subjects were randomly assigned to one of the two dosing sequences.

The concentration of monomethyl fumarate was measured from plasma samples collected over a 24-hour interval after dosing in each period. Pharmacokinetic parameters C_{max} , T_{max} , AUC_t , AUC_{inf} , $AUC_{\%extrap}$, $T_{1/2}$ and λ were estimated based on plasma levels of monomethyl fumarate for subjects included in the statistical analysis.

Number of Subjects (planned and analyzed)

Sixteen (16) subjects were enrolled, received doses in both periods and completed the study as planned.

All plasma samples from sixteen (16) subjects were analyzed by the bioanalytical laboratory. All concentration data of monomethyl fumarate (MMF) from sixteen (16) subjects were included in the pharmacokinetic and statistical analysis.

Demographics

Table 12: Applicant Table, Demographics, Study BLS-11-108

	Age	Height (cm)	Weight (kg)	BMI	Race/Ethnicity	
Mean	43.3	170.2	74.5	25.7	White	5
+/- SD	15.9	8.5	11.7	3.7	Black	11
Median	40.5	172.1	77.5	26.5	Asian	0
					Native	0
Range	23.0-74.0	156.2-185.6	51.9-89.7	18.6-29.9	Hispanic/ Latino	0

Source: CSR Study BLS-11-108, page 41

Diagnosis and Main Criteria for Inclusion

All subjects enrolled in this study were judged by the Principal Investigator (PI) to be normal, healthy volunteers who met all inclusion and none of the exclusion criteria.

Study Treatments

Treatment A: Monomethyl Fumarate 95 mg Delayed Release Capsules; Lot No: 14700847MA; (Banner Life Sciences 4125 Premier Drive, High Point, NC 27265)

Dose: 1 x 95 mg

Mode of Administration: Oral under Fasting conditions

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Treatment B: Monomethyl Fumarate 95 mg Delayed Release Capsules; Lot No: 14700847MA;
(Banner Life Sciences 4125 Premier Drive, High Point, NC 27265)

Dose: 2 x 95 mg

Mode of Administration: Oral under Fasting conditions

Duration of Treatment

The study consisted of two study periods. Each study period included a single-dose drug administration of either 1 x 95 mg or 2 x 95 mg of the Test product. There was a washout period of at least 72 hours between each drug administration. Subjects were confined to the clinic the day prior to dosing until approximately 24 hours post-dose.

Criteria for Evaluation

Pharmacokinetics: Serial blood samples for measurement of MMF plasma concentrations were collected over a 24- hour period (please note that different sampling schedules were followed for the fed and fasted treatment conditions: The plasma concentration-time data for MMF was analyzed using non-compartmental methods. The plasma PK parameters of interest following (treatment A) a single dose of BLS-11 95 mg (1 x 95 mg) MMF and (treatment B) a single dose of BLS-11 190 mg (2 x 95 mg) MMF included: AUC_{0-t} , AUC_{0-inf} , $AUC_{\%extrap}$, C_{max} , t_{max} , K_{el} , t_{lag} , and $t_{1/2}$.

Safety: Safety was evaluated by vital signs measurement [blood pressure (BP) and heart rate (HR)], clinical laboratory tests (including hematology, urine analysis, serum chemistry), pregnancy test (females only), physical examinations and adverse events reported by subjects who received a drug treatment.

Statistical Methods

Descriptive statistics (min, max, median, mean, standard deviation, and coefficient of variation) of all pharmacokinetic parameters were provided for treatment A and treatment B. Analysis of Variance (ANOVA) was conducted to compare the dose-normalized (to 95 mg) PK parameters of monomethyl fumarate between treatments, using natural log-transformed C_{max} , AUC_t , and AUC_{inf} . The ANOVA model included sequence, period, and treatment as a fixed effect term, subjects nested within sequence as random effect.

The point estimate and 90% confidence intervals (CI) for the Treatment B / Treatment A, ratios of geometric least-squares means for C_{max} , AUC_t , and AUC_{inf} , were calculated after exponentiation of the difference in least squares means (Treatment B – Treatment A).

Results

Pharmacokinetic Results

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Per the applicant's study synopsis:

“The statistical analysis of dose-normalized PK parameters of MMF showed that administration of one and two capsules of BLS-11 95 mg delayed release capsules generated dose proportional increases in AUC_t and AUC_{inf} of MMF. The 90% confidence interval (CI) for AUC_t and AUC_{inf} parameter geometric least squares means (GLSM) ratios were contained within 80.00% - 125.00%. The C_{max} of MMF also increased nearly dose proportionally from one to two capsules, however, because of the large intra-subject variability (37.05%) and a sample size of 16 subjects, the 90% confidence interval for dose normalized C_{max} GLSM ratio, 2 capsules vs. 1 capsule, was slightly outside the 80 to 125% confidence interval.

“Overall, the results supported that plasma exposure to MMF is dose proportional following administration of BLS-11 95 mg MMF delayed release capsules.”

Safety Results

A total of forty mild AEs were experienced by 10 subjects (62.5%) who received BLS-11 95 mg. All AEs were deemed related to the study medication.

A total of thirty mild AEs were experienced by 7 subjects (43.8%) who received BLS 190 mg. All AEs were deemed related to the study medication.

No serious AEs were reported during the conduct of this study. There were no deaths reported during the conduct of this study.

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Table 13: Applicant Table, Adverse Events, Study BLS-11-108

MEDDRA SYSTEM ORGAN CLASS NAME MEDDRA PREFERRED TERM NAME	Treat A (N=16)	Treat B (N=16)
Any Treatment Emergent Adverse Events	10 (62.5%)	7 (43.8%)
Gastrointestinal disorders	1 (6.3 %)	0 (0.0 %)
Abdominal pain	1 (6.3 %)	0 (0.0 %)
Diarrhoea	1 (6.3 %)	0 (0.0 %)
General disorders and administration site conditions	1 (6.3 %)	0 (0.0 %)
Feeling hot	1 (6.3 %)	0 (0.0 %)
Nervous system disorders	2 (12.5%)	0 (0.0 %)
Dizziness	2 (12.5%)	0 (0.0 %)
Headache	1 (6.3 %)	0 (0.0 %)
Skin and subcutaneous tissue disorders	2 (12.5%)	0 (0.0 %)
Pruritus	2 (12.5%)	0 (0.0 %)
Vascular disorders	8 (50.0%)	7 (43.8%)
Flushing	8 (50.0%)	7 (43.8%)

Treatment A: 1 × 95 mg Monomethyl Fumarate Delayed-Release Capsule

Treatment B: 2 × 95 mg Monomethyl Fumarate Delayed-Release Capsules

Reviewer Comment: Study BLS-11-108 revealed no significant or novel safety findings. Please refer to the PK review for further discussion of the dose proportional serum concentration findings.

6. Review of Relevant Individual Trials Used to Support Efficacy

This NDA was submitted via the 505(b)(2) registration pathway. No clinical efficacy studies were conducted with BLS-11. This 505(b)(2) application, supported by PK bridging studies, therefore, relies entirely on the findings of clinical efficacy reported for Tecfidera under NDA 204063.

The following table is reprinted from the Clinical Review for NDA 204063 and demonstrates the key findings that supported efficacy of Tecfidera.

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Table 14: Efficacy Results of Annualized Relapse Rate and Proportion Relapsing, Intention-To-Treat population of Tecfidera Pivotal Trials

Trial 301				Trial 302				
Endpoint	Placebo	240 mg bid	240 mg tid	Endpoint	Placebo	240 mg bid	240 mg tid	GA
Proportion relapsing*	0.461	0.270 p<0.0001	0.260 p<0.0001	ARR	0.401	0.224 p<0.0001	0.198 p<0.0001	0.286 p<0.0001
ARR	0.364	0.172 p<0.0001	0.189 p<0.0001	Proportion relapsing	0.41	0.291 p=0.002	0.241 p<0.001	0.321 p=0.0097

*Bolded row above represents results for the primary endpoint of the trial

Source: Clinical Review of NDA 204063 authored by Heather Fitter, M.D., page 94

7. Integrated Review of Effectiveness

As noted above, this NDA is a 505(b)(2) application supported by PK bridging studies to demonstrate bioequivalence. This NDA relies on the findings of clinical efficacy for the listed drug, Tecfidera (under NDA 204063), for support of efficacy. There were no efficacy studies and the applicant collected no efficacy data in the PK bridging studies.

7.1. Additional Efficacy Considerations

7.1.1. Considerations on Benefit in the Postmarket Setting

This NDA is a 505(b)(2) application and therefore provides no efficacy data and instead relies on the equivalence of BLS-11 to fully metabolized DMF (the listed drug, Tecfidera) to support a claim of effectiveness. This claim of equivalence appears justified based on the pharmacokinetic data and nonclinical literature submitted in support of this NDA. However, it remains possible that in a future review of clinical experience that Bafiertam may have demonstrably different efficacy than that of the listed drug, Tecfidera. Any observed difference would be presumably attributable to the absence of whatever contributory effects exist for DMF that would be present only in the listed drug, Tecfidera. Therefore, reports of relapses, increased lesion burden, and accumulating disability that are out of proportion to those reported with the listed drug should be noted and evaluated further to confirm the postulated equivalency or to ascertain whether there are clinically relevant differences in the clinical outcomes of treatment with BLS-11 versus Tecfidera.

7.1.2. Other Relevant Benefits

There do not appear to be any additional benefits claimed or observed for Bafiertam other than what is claimed for the listed drug, Tecfidera.

7.2. Integrated Assessment of Effectiveness

The efficacy of Bafiertam is predicted to be equivalent to that of the listed drug, Tecfidera.

8. Review of Safety

8.1. Safety Review Approach

The applicant did not conduct Phase 3 studies to support safety, and thus the clinical safety database from the PK studies conducted by the applicant are the primary and only sources of novel data for the clinical safety review. As this is a 505(b)(2) application, the safety conclusions ultimately rely on the safety findings in the listed drug application. I provide the safety findings for single doses of BLS-11 alongside the findings with the listed drug when possible to demonstrate similarity. I discuss differences between BLS-11 and the listed drug when appropriate. The labeling for the listed drug, Tecfidera, will serve as a template for the labeling of Bafiertam.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Safety Population Exposure

The applicant defined the Safety Population as all participants under any fed condition (fasted and not fasted) in the five Phase 1 clinical studies that the applicant conducted using the 200 mg market formulation BLS-11 product. The majority of the included patients received a single dose of BLS-11. The applicant stated, "because the majority of the safety experience with MMF can be traced back to the administration of DMF, postmarketing reports of AEs associated with administration of Tecfidera are also considered."

Reviewer Comment: I requested the safety data from all seven studies conducted using MMF, including the 214 mg and various 200 mg formulations that the applicant will not market. My safety tables include all safety data from all seven trials unless otherwise noted.

Table 15: Reviewer Table, Unique Patients, All Studies

Clinical Trial Groups	BLS-11 (any dose, any formulation)	DMF (Tecfidera)
Healthy volunteers	204	147
Controlled trials in MS	0	2665
Controlled trials in psoriasis	0	320
Controlled trials in rheumatoid arthritis	0	101

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Sources: ISS page 39 and Safety Review NDA 204063 page 16

I summarize subject exposure by doses below and accounts for multiple exposures within the same patient as unique events:

Table 16: Reviewer Table, Duration of Exposure to BLS-11 (all doses)

Dosage	Number of patients exposed to the study drug:				
	1 dose	2 doses	≥6 months	≥12 months	≥18 months
<i>BLS-11 214 mg</i>	N=48	N=0	N=0	N=0	N=0
<i>BLS-11 200 mg*</i>	N=98	N=0	N=0	N=0	N=0
<i>BLS-11 190 mg</i>	N=145	N=39	N=0	N=0	N=0
<i>BLS-11 95 mg</i>	N=16	N=0	N=0	N=0	N=0

Source: ISS, page 39

* includes all BLS-11 formulations containing 200 mg MMF

Reviewer Comment: The submitted patient exposure numbers do not meet the ICH guidelines for chronically administered medications (i.e., n=100 for 1 year). However, this NDA is submitted as a 505(b)(2) application and derives its safety findings from the listed drug, Tecfidera, and as such, the failure to meet ICH guideline criteria is not an issue of review because the studies submitted to support approval of the listed drug did satisfy the ICH criteria.

I provide the following table in order to clarify the patient exposures to MMF in the studies provided to support this application. All seven studies employed crossover designs; consequently, patients had multiple exposures per study.

Table 17: Reviewer Table, Patient Exposures by Study, All Patients

Study	Enrolled Patients	BLS-11 214 mg Fasted	BLS-11 200 mg Fasted	BLS-11 190 mg Fasted	BLS-11 190 mg Fed	BLS-11 95 mg Fasted	BLS-11 All	Tecfidera 200 mg Fasted
BLS-11-101	24	48*	24					24
BLS-11-102	24	48*	24					24
BLS-11-103	50		50					50
BLS-11-104	50			50				49**
BLS-11-105	16			16	16			
BLS-11-106	24			23†	23‡			
BLS-11-108	16			16		16		
Total for safety evaluation	204	96	98	105	39	16	354	147

* Studies BLS-11-101 and BLS-11-102 used two different formulations of MMF 214 mg; patients were exposed twice to 214 mg MMF in these studies.

** One patient in Study BLS-11-104 discontinued the study for personal reasons and did not receive a dose of Tecfidera.

† One patient in Study BLS-11-106 discontinued the study due to nausea/vomiting after receiving BLS-11 in the fed state and did not receive a dose of BLS-11 in the fasted state

‡ One patient in Study BLS-11-106 failed to return for the BLS-11 90 mg fed status treatment but had received the fasted BLS-11 90 mg treatment.

Reviewer Comment: The applicant used a crossover trial design meaning that in any study the same group of patients would receive all treatments in that study. All the studies' designs ensured a washout period of at least five days between each treatment. The half-life in vivo of MMF (and DMF) is approximately twelve hours. Thus, five days

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would represent at least ten halves between treatments and should have ensured no possibility of carry-over effects. Any adverse event that occurred after a treatment but before the next treatment in a sequence was assigned to the preceding treatment. Therefore, in the subsequent tables reviewing safety data, I will treat the same patient receiving different treatments more than five days apart as distinct exposures.

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8.2.2. Relevant characteristics of the safety population:

The applicant performed Phase 1 studies in a population of individuals with no significant health issues. The demographic subsets of the entire population exposed to BLS-11 in these studies are below.

Table 18: Reviewer Table, Summary of Exposures by Demographic Data, All Patient Exposures

	BLS-11 95 mg Fasted (N=16)	BLS-11 190 mg Fasted (N=105)	BLS-11 190 mg Fed (N=39)	BLS-11 200 mg Fasted (N=98)	BLS-11 214 mg Fasted (N=96)	BLS-11 95-200 mg Combined (N=354)	Tecfidera 240 mg (N=147)
Age at Consent							
N	16	105	39	98	96	354	147
Mean	43	37	34	38	37	37	37
SD	15.9	10.8	9.2	10.7	11.2	11.0	10.2
Median	41	36	35	40	34	36	37
Min, Max	23, 74	20, 74	20, 52	19, 56	19, 56	19, 74	19, 56
Age Categories							
< 37	8 (50%)	57 (54%)	23 (59%)	45 (46%)	54 (56%)	187 (53%)	71 (48%)
≥ 37	8 (50%)	48 (46%)	16 (41%)	53 (54%)	42 (44%)	167 (47%)	76 (52%)
Gender							
Male	9 (56%)	63 (60%)	17 (44%)	52 (53%)	64 (67%)	205 (58%)	87 (59%)
Female	7 (44%)	42 (40%)	22 (56%)	46 (47%)	32 (33%)	149 (42%)	60 (41%)
Race							
White	5 (31%)	77 (73%)	34 (87%)	54 (55%)	20 (21%)	190 (54%)	92 (63%)
Non-	11 (69%)	28 (27%)	5 (13%)	44 (45%)	76 (79%)	164 (46%)	55 (37%)
Ethnicity							
Hispanic	0	54 (51%)	28 (72%)	36 (37%)	2 (2%)	120 (34%)	63 (43%)
Not Hispanic	16 (100%)	51 (49%)	11 (28%)	62 (63%)	94 (98%)	234 (66%)	84 (57%)
Height (cm)							
N	16	105	39	98	96	354	147
Mean	170	168	165	168	172	169	169
SD	8.5	9.1	8.9	10.7	9.8	9.9	10.2
Median	172	169	164	169	171	169	169
Min, Max	156, 186	150, 198	150, 189	146, 193	153, 193	146, 198	146, 198
Weight (kg)							
N	16	105	39	98	96	354	147
Mean	74.5	72.6	70.0	74.6	78.3	74.5	74.3
SD	11.74	11.23	11.24	12.25	12.68	12.18	11.84
Median	77.5	72.6	68.8	75.8	79.7	74.6	74.0
Min, Max	51.9, 89.7	46.6, 100.5	47.5, 93.7	50.6, 105.1	50.6, 105.1	46.6, 105.1	46.6, 105.1
BMI (kg/m ²)							
N	16	105	39	98	354	210	99
Mean	25.72	25.62	25.57	26.21	26.01	25.70	25.80

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SD	3.65	2.89	2.92	2.70	2.87	2.87	2.61
Median	26.50	25.81	26.00	26.82	26.43	25.94	25.81
Min, Max	18.60, 29.90	18.60, 29.90	18.72, 29.83	18.90, 29.90	18.60, 29.90	18.60, 29.90	19.10, 29.62

Source: ISS, Table 3-2, pages 38-39, ISS Supplement pages 2-3, Information Request response dated 1—5-2018, and ADSL.xpt and revised ADSL.xpt submitted in response to Information Request dated 11-04-2018

Reviewer Comment: As a 505(b)(2) study, the safety data rely on the safety findings in the approved application for the listed drug. The population exposed to BLS-11 and Tecfidera appear to be similar on all noted characteristics. The population used in the Phase 1 studies to support the pharmacological bridging and fed status studies is healthy, more than half are male, and more than half are younger than age 37. This population does represent the population with multiple sclerosis, which is predominantly women older than 35 years old.⁹ There is an expectation that the safety for BLS-11 will not differ significantly than that of the listed drug when used in the intended population, however, and no obvious safety signal emerged in different demographic subgroups evaluated in the studies submitted with this NDA.

8.2.3. Adequacy of the safety database:

The adequacy of the safety database for BLS-11 is not relevant because this application relies on the previously accepted safety database for the listed drug, Tecfidera.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

There are no issues regarding data integrity and submission quality. The application is of sufficient quality to permit review. The applicant responded promptly to information requests. I was able to replicate the safety findings made by the Applicant using the data sets supplied in the application and those obtained by Information Requests.

8.3.2. Categorization of Adverse Events

The applicant mapped adverse events to the Medical Dictionary for Regulatory Activities (MedDRA) version 19.1 preferred term and system organ classification. Treatment-emergent Adverse Events (TEAEs) included any AEs that began or worsened after the start of study drug. TEAEs were summarized according to the treatment received at the time the event began. Events with a start date from the start of drug in Period 1 until the time just prior to the start of drug in Period 2 were assigned to the treatment received in Period 1. Events with a start date from the start of drug in Period 2 until the follow-up assessment were assigned to the treatment received in Period 2.

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The applicant summarized the occurrence of TEAEs by treatment group and severity using SOC and PTs. If a subject experienced multiple events within a given treatment exposure that mapped to a single PT, the maximal severity grade and strongest investigator assessment of the relationship to study drug were assigned to the PT.

The applicant generated summary presentations of TEAEs by SOC and PT, TEAEs by severity, and TEAEs by relationship to study medication.

Gastrointestinal tolerability was an adverse event of special interest in the individual study analyses and reports, and thus gastrointestinal TEAEs were included in the integrated analysis. GI tolerability was defined as all TEAEs pertaining to the following: nausea, vomiting, diarrhea, constipation, and abdominal pain. Specific MedDRA coded terms were included in these individual evaluations, and I collapsed similar terms in an effort to determine whether a more general safety signal was present. These collapsed terms included “abdominal pain” (abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness, abdominal distension, abdominal discomfort and suprapubic pain), “nausea and vomiting,” and “diarrhea” (diarrhea and flatulence). These events were summarized by event type (abdominal pain, nausea, vomiting, constipation, and diarrhea) and by their preferred terms.

Additionally, summaries of TEAEs appearing in the standard MedDRA query (SMQ), gastrointestinal nonspecific symptoms and therapeutic procedures, were summarized by SOC and PT.

8.3.3. Routine Clinical Tests

Standard clinical laboratory profiles for hematology, serum chemistry, and urinalysis were evaluated for all subjects at screening, check-in for Period 1 (Day -1) and Day 2 of Period 2, or upon early termination in each study. As such, only the Day 2 of Period 2 evaluations are captured following the initiation of study drug. These values were summarized according to the treatment received in Period 2. The baseline value was taken as the Period 1 (Day -1) value in this case. If this value was missing, the Screening value could be considered as baseline.

Where necessary, units were converted to a standard unit prior to summarization. Normal ranges were determined based on the ranges supplied by the laboratory (with appropriate conversion to obtain standard units) and were not normalized. Missing normal ranges could be replaced by standard laboratory ranges. The severity of laboratory abnormalities were graded according to the Division of AIDS (DAIDS) Table for grading the severity of Adult and Pediatric Adverse Events (publish date: December 2004, with clarification August 2009).

I summarized white blood cell (WBC) counts, as well as the change from baseline, by treatment group using descriptive statistics. The applicant summarized the number and percentage of subjects experiencing treatment-emergent DAIDs Grade 3-4 laboratory values by maximal grade and treatment group.

The applicant summarized vital signs (sitting systolic blood pressure, sitting diastolic blood pressure, sitting pulse, and temperature) by treatment group using descriptive statistics. For each vital sign, I present the baseline, 2-hours post-dose, and 24-hours post-dose assessments. The applicant calculated descriptive statistics for the observed values, as well as the change from baseline values.

8.3.5. Electrocardiograms

The applicant obtained a single 12-lead electrocardiograms (ECGs) at screening and at 2 hours prior to dosing with any treatment in Period 1 of each study.

8.4. Safety Results

8.4.1. Deaths

There were no deaths reported in association with any of the studies included in this application.

8.4.2. Serious Adverse Events

There were no serious adverse events reported during the studies included in this application.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

One subject experienced an AE that led to discontinuation during Study BLS-11-106. The subject was a 27-year-old Hispanic woman in the Treatment Sequence Fed/Fasted. She experienced an AE of vomiting (mild) that began 8.3 hours after receiving 190 mg of BLS-11 in the “fed” condition. She experienced flushing (mild) 7 hours after dosing. She reported nausea (mild) 7 minutes prior to one episode of vomiting. Her nausea improved after vomiting. Because her vomiting occurred within 14.5 hours after dosing, she was subsequently discontinued from the study per protocol. All of the subject’s AEs resolved without treatment. The investigator considered the AEs of flushing, nausea, and vomiting to be likely related to the study drug.

There were no other reported discontinuations due to AEs in these seven studies.

There were other discontinuations. One patient discontinued Study BLS-11-104 for personal reasons unrelated to the trial and not related to an AE. One patient in Study BLS-11-106 did not return for the second assigned treatment. One patient in Study BLS-11-106 failed to return for the follow-up visit.

Reviewer Comment: According to the labeling for the listed drug this application relies upon, nausea and vomiting occur at incidences of 12% and 9%, respectively, after

administration of DMF. Therefore, nausea and vomiting are expected adverse events after administration for BLS-11. A single patient discontinuation for vomiting is therefore not an unexpected AE. The discontinuation for personal reasons does not appear related to study treatment. I lack sufficient information regarding the two discontinuations for not showing up for appointments to generate any conclusions about their reasons for discontinuing the study.

8.4.4. Treatment Emergent Adverse Events and Adverse Reactions

Review of all subjects who received BLS-11 reveals an overall similarity in TEAEs reported in comparison to the group dosed with the listed drug, Tecfidera.

Considering all TEAEs, 47% of subjects dosed with BLS-11 reported at least one TEAE (range 29%-67%) in comparison to 51% of subjects dosed with Tecfidera who reported at least one TEAE.

The most common Preferred Term TEAE reported in all subjects who received BLS-11 or Tecfidera was “flushing.” Combining all BLS-11 studies, 145 out of 354 exposed patients (41%) in a BLS-11 treatment group reported flushing. Among subjects treated with Tecfidera, 75 out of 147 (51%) of subjects reported flushing.

The applicant focused on gastrointestinal TEAEs and reported for the Gastrointestinal Disorders SOC as a whole, TEAEs within this SOC occurred in 6% (23 exposed patients) of the total 354 BLS-11 subject exposures compared with 7% (11/147 subjects) of those exposed to Tecfidera. Within the Gastrointestinal Disorders SOC, the most common reported preferred term TEAE was nausea, which occurred in 7/210 (2%) of BLS-11 exposures and 5/147 (3%) of Tecfidera exposures.

Treatment-emergent AEs within the Nervous System Disorders SOC occurred at slightly over twice the incidence in subjects following administration of BLS-11 at any dose (18/354, 5%) than occurred in the Tecfidera exposed subjects (3/147, 2%). Subject exposed to the 190 mg of MMF in the fed state reported headaches at a greater incidence (3/39, 8%) than in the fasted state (0/105, 0%). Overall, in all MMF exposed patients, the headache incidence rate was 8/354 (2%)

The TEAEs from all studies of BLS-11 are listed below. Discussions of the TEAEs across different demographic subgroups are found in Section 8.6.

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Table 19: Reviewer Table, Treatment-Emergent Adverse Event Frequency by System Organ Class and Preferred Term, All Studies, All Exposed Patients

System Organ Classification	BLS-11 95 mg Fasted (n=16)	BLS-11 190 mg Fasted (n=105)	BLS-11 190 mg Fed (n=39)	BLS-11 200 mg Fasted (n=98)	BLS-11 214 mg Fasted (n=96)	BLS-11 All* (n=354)	Tecfidera 240 mg (n=147)
Preferred Term							
Any AE	10 (63%)	60 (57%)	26 (67%)	43 (44%)	28 (29%)	167 (47%)	75 (51%)
Vascular Disorders	8 (50%)	58 (55%)	22 (56%)	32 (33%)	25 (26%)	145 (41%)	65 (44%)
Flushing	8 (50%)	58 (55%)	22 (56%)	32 (33%)	25 (26%)	145 (41%)	65 (44%)
General Disorders & Administration Site Conditions	1 (6%)	4 (4%)	5 (13%)	6 (6%)	1 (1%)	17 (5%)	4 (3%)
Feeling hot	1 (6%)	1 (1%)	3 (8%)	1 (1%)	0	6 (2%)	0
Vessel puncture site pain	0	0	0	3 (3%)	1 (1%)	4 (1%)	3 (2%)
Chills	0	2 (2%)	0	0	0	2 (1%)	0
Vessel puncture site swelling	0	0	0	2 (2%)	0	2 (1%)	1 (1%)
Catheter site edema	0	1 (1%)	0	0	0	1 (1%)	0
Catheter site pain	0	1 (1%)	0	0	0	1 (1%)	0
Infusion site pain	0	0	1 (3%)	0	0	1 (1%)	0
Suprapubic pain	0	0	0	1 (1%)	0	1 (1%)	0
Vessel puncture site hemorrhage	0	0	1 (3%)	0	0	1 (1%)	2 (1%)
Vessel puncture site induration	0	0	0	1 (1%)	0	1 (1%)	0
Vessel puncture site erythema	0	0	0	0	0	0	1 (1%)
Gastrointestinal Disorders	1 (6%)	4 (4%)	5 (13%)	9 (9%)	5 (5%)	24 (7%)	12 (8%)
Nausea	0	0	1 (3%)	3 (3%)	3 (3%)	7 (2%)	5 (3%)
Abdominal pain	1 (6%)	1 (1%)	0	1 (1%)	1 (1%)	4 (1%)	2 (1%)
Diarrhea	1 (6%)	1 (1%)	0	1 (1%)	1 (1%)	4 (1%)	5 (3%)
Abdominal pain upper	0	0	1 (3%)	2 (2%)	0	3 (1%)	2 (1%)
Vomiting	0	0	1 (3%)	0	2 (2%)	3 (1%)	0
Abdominal discomfort	0	1 (1%)	1 (3%)	0	0	2 (1%)	1 (1%)
Abdominal distension	0	0	1 (3%)	1 (1%)	0	2 (1%)	2 (1%)
Constipation	0	0	2 (5%)	0	0	2 (1%)	0

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Abdominal pain lower	0	0	0	1 (1%)	0	1 (1%)	0
Abdominal tenderness	0	0	0	1 (1%)	0	1 (1%)	0
Chapped lips	0	1 (1%)	0	0	0	1 (1%)	1 (1%)
Dyspepsia	0	0	0	0	0	0	1 (1%)
Flatulence	0	0	0	0	0	0	1 (1%)
Nervous System Disorders	2 (13%)	1 (1%)	4 (10%)	10 (10%)	1 (1%)	19 (5%)	3 (2%)
Headache	1 (6%)	0	3 (8%)	4 (4%)	0	8 (2%)	3 (2%)
Dizziness	2 (13%)	1 (1%)	0	2 (2%)	0	5 (1%)	0
Presyncope	0	0	0	2 (2%)	0	2 (1%)	0
Hypoaesthesia	0	1 (1%)	0	0	0	1 (1%)	0
Paresthesia**	0	0	1 (3%)	0	1 (1%)	1 (1%)	0
Somnolence	0	0	0	1 (1%)	0	1 (1%)	0
Tremor	0	0	0	1 (1%)	0	1 (1%)	0
Skin & Subcutaneous Tissue Disorders	2 (13%)	2 (2%)	3 (8%)	4 (4%)	2 (2%)	13 (4%)	5 (3%)
Pruritus	2 (13%)	1 (1%)	0	4 (4%)	2 (2%)	9 (3%)	5 (3%)
Pruritus generalized	0	1 (1%)	2 (5%)	0	0	3 (1%)	0
Erythema	0	0	1 (3%)	0	0	1 (1%)	0
Rash macular	0	0	0	1 (1%)	0	1 (1%)	0
Rash papular	0	0	0	1 (1%)	0	1 (1%)	0
Cardiac Disorders	0	1 (1%)	0	0	0	1 (1%)	0
Palpitations	0	1 (1%)	0	0	0	1 (1%)	0
Ear & Labyrinth Disorders	0	0	1 (3%)	0	0	1 (1%)	0
Tinnitus	0	0	1 (3%)	0	0	1 (1%)	0
Eye Disorders	0	0	0	1 (1%)	0	1 (1%)	0
Eye irritation	0	0	0	1 (1%)	0	1 (1%)	0
Injury, Poisoning, & Procedural Complications	0	1 (1%)	0	0	0	1 (1%)	0
Procedural anxiety	0	1 (1%)	0	0	0	1 (1%)	0
Musculoskeletal & Connective Tissue Disorders	0	0	0	2 (2%)	1 (1%)	3 (1%)	1 (1%)
Arthralgia	0	0	0	1 (1%)	0	1 (1%)	0
Back Pain	0	0	0	1 (1%)	0	1 (1%)	0
Neck Pain	0	0	0	0	1 (1%)	1 (1%)	0

Muscle spasms	0	0	0	0	0	0	1 (1%)
Psychiatric Disorders	0	1 (1%)	0	0	0	1 (1%)	0
Anxiety	0	1 (1%)	0	0	0	1 (1%)	0
Euphoric mood	0	1 (1%)	0	0	0	1 (1%)	0
Reproductive System & Breast Disorders	0	1 (1%)	0	0	0	1 (1%)	0
Metrorrhagia	0	1 (1%)	0	0	0	1 (1%)	0
Respiratory, Thoracic, & Mediastinal Disorders	0	1 (1%)	0	0	0	1 (1%)	2 (1%)
Rhinorrhea	0	1 (1%)	0	0	0	1 (1%)	0
Nasal congestion	0	0	0	0	0	0	2 (2%)

Sources: Summary of Safety, Table 3-3, page 42, ISS Supplement pages 3-4, Table 2.1 in Information Request response October 23, 2018, and ADAE.xpt

*The BLS-11 All Exposed column is the number of exposures to BLS-11 under any condition. Serial treatments in the same subject are considered independent observations.

** paresthesia includes paresthesia and burning sensation

Reviewer Comment: Including all patients from all studies did not create a significant difference in the adverse event profile of BLS-11 as compared with the profile submitted by the applicant for only five of the seven studies. Overall, there are two significant limitations to these safety findings. As noted above, the patient population is small and not representative of the intended treatment population. Secondly, most of these findings follow a single acute dose of BLS-11, and the intended dosing regimen will be chronic daily administration over periods of months or years. Nevertheless, there is utility to comparative analysis of adverse events following acute doses of BLS-11 and the listed drug, and overall, the adverse events reported by patients taking single doses of BLS-11 appear similar to those reported by patients. The similarity between the adverse event profiles of MMF and Tecfidera is reassuring given the hypothesis that MMF is the primary driver of Tecfidera's clinical effects. Subjects reported that flushing was the most common TEAE. Flushing is a commonly reported side effect indicated on labeling of the listed drug, Tecfidera. Patients exposed to BLS-11 reported twice the incidence of headaches as Tecfidera-exposed patients (5% versus 2%), but the reported incidence for headache is below the reported incidence of 6% on Tecfidera labeling. Other neurological symptoms reported in these acute dose studies (paresthesia, hypoesthesia, dizziness) had been noted in Tecfidera's larger safety database, and at much higher rates (6%, 5%, and 4%, respectively as compared to 1%, 1%, and 1% in all BLS-11 studies, respectively.) Constipation was reported in 1% of BLS-11 exposed patients, and no patients exposed to Tecfidera noted constipation. In the Tecfidera approval data, 3% of patients experienced constipation, and there was suggestion of dose-dependency because increasing dosing

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frequency from every twelve to every eight hours was associated with a 1% rise in reported constipation rates (from 3% to 4%). Thus, it is likely that constipation is, and will remain, an adverse event when patients will take BLS-11 on a daily basis, and it is likely that the observed lack of Tecfidera-associated constipation is spurious, either because of small numbers exposed, because dosing was not chronic, or because of both reasons. Other gastrointestinal-specific adverse events are discussed in 8.5.1. Sub-analysis of the different BLS-11 doses used in these trials did not reveal a dose-dependent effect for BLS-11 with respect to any of the noted TEAEs when the 95 mg dose was compared to the 190 mg and 200 mg doses, but it should be noted only 16 patients received the 95 mg dose of BLS-11, and thus interpretation is limited by a small comparative sample size.

TEAE Severity

Most of the TEAEs reported in all of the BLS-11 studies were designated as “mild.” Occurrence incidence of “mild” TEAEs between groups was similar, 44% of patients exposed to any dose of BLS-11 experienced a “mild” TEAE, and in 48% exposed to the listed drug, Tecfidera, reported a “mild” TEAE.

Patients exposed to either BLS-11 or the listed drug reported “moderate” severity TEAEs at an incidence rate of 2%. As shown in the table below, the most frequently reported “moderate” TEAE was “headache” and fasted patients exposed to BLS-11 190 mg reported the highest incidence (3/39 or 8%) of “moderate” severity headaches.

There were no “severe” adverse events and no events deemed to be “life-threatening” in either exposure group.

Table 20: Reviewer Table, Severity of Most Common Treatment-Emergent Adverse Events Preferred Terms by System Organ Class and Preferred Term, All Studies

System Organ Classification	BLS-11 95 mg Fasted (n=16)	BLS-11 190 mg Fasted (n=105)	BLS-11 190 mg Fed (n=39)	BLS-11 200 mg Fasted (n=98)	BLS-11 214 mg Fasted (n=96)	BLS-11 All* (n=354)	Tecfidera 240 mg (n=147)
Preferred Term							
Any TEAE	10 (63%)	60 (57%)	26 (67%)	43 (44%)	28 (29%)	167 (47%)	75 (51%)
Any Mild TEAE	10 (63%)	59 (56%)	26 (67%)	43 (44%)	25 (26%)	157 (44%)	71 (48%)
Any Moderate TEAE	0	1 (1%)	0	6 (6%)	3 (3%)	10 (3%)	4 (3%)
Any Severe TEAE	0	0	0	0	0	0	0
Vascular Disorders (and	8	58	22	32	25	145	65 (44%)

grade)	(50%)	(55%)	(56%)	(33%)	(26%)	(41%)	
Flushing (any grade)	8 (50%)	58 (55%)	22 (56%)	32 (33%)	25 (26%)	145 (41%)	65 (44%)
Mild	8 (50%)	58 (55%)	22 (56%)	32 (33%)	25 (26%)	145 (41%)	65 (44%)
Gastrointestinal Disorders (any grade)	1 (6%)	4 (4%)	5 (13%)	9 (9%)	5 (5%)	24 (7%)	12 (8%)
Mild	1 (6%)	4 (4%)	5 (13%)	8 (8%)	2 (2%)	20 (6%)	10 (7%)
Moderate	0	0	0	1 (1%)	3 (3%)	4 (1%)	2 (1%)
Nausea (any grade)	0	0	1 (3%)	3 (3%)	3 (3%)	7 (2%)	5 (3%)
Mild	0	0	1 (3%)	3 (3%)	3 (3%)	7 (2%)	5 (3%)
Vomiting (any grade)	0	0	1 (3%)	0	2 (2%)	3 (1%)	0
Mild	0	0	1 (3%)	0	0	1 (0%)	0
Moderate	0	0	0	0	2 (2%)	2 (1%)	0
Constipation	0	0	2 (5%)	0	0	2 (1%)	0
Mild	0	0	2 (5%)	0	0	2 (1%)	0
Diarrhea (any grade)	1 (6%)	1 (1%)	0	1 (1%)	1 (1%)	4 (1%)	5 (3%)
Mild	1 (6%)	1 (1%)	0	0	0	2 (1%)	4 (3%)
Moderate	0	0	0	1 (1%)	1 (1%)	2 (1%)	1 (1%)
Nervous System Disorders (any grade)	2 (13%)	1 (1%)	4 (10%)	10 (10%)	1 (1%)	18 (5%)	3 (2%)
Headache	1 (6%)	0	3 (8%)	4 (4%)	0	8 (2%)	3 (2%)
Mild	1 (6%)	0	3 (8%)	1 (1%)	0	5 (1%)	1 (1%)
Moderate	0	0	0	3 (3%)	0	3 (1%)	2 (1%)

Sources: Summary Clinical Safety Table 3-4 page 47, revised ISS Table 3.1, and revised ADAE.xpt

Reviewer Comment: As discussed above, while patients reported headaches more often in a BLS-11 treatment condition, the overall incidence rate of headache was lower in both groups than had been noted in a larger safety database for the listed drug. Gastrointestinal Disorders AEs occurred at similar incidences in the BLS-11 and Tecfidera treatment groups and below rates reported for the listed drug and are expected to be more common in the target population. Fed status appeared to confer a larger risk of gastrointestinal disorders (13%) compared to fasted status incidence rate (4%) in the 190 mg BLS-11 dose treatment, albeit with a small sample size for the fed status population. No significant new safety issues of any severity emerged in these single dose exposure studies.

8.4.5. Laboratory Findings

The applicant performed clinical laboratory tests at screening and after dosing. There were no

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serious or potentially life-threatening laboratory abnormalities noted in any of the studies included in this NDA. All mean serum chemistry, hematology, and urinalysis parameters in the study were within reference range at all post-dose time points.

The applicant reported that twelve subjects exhibited transient shifts in serum hemoglobin from normal reference range values at Day –1 of Period 1 to a value below reference range on Day 2 of Period 2, including nine subjects receiving Tecfidera followed by BLS-11 and three subjects receiving BLS-11 followed by Tecfidera. The lowest value noted was 11.1 g/dL, with the lower limit of normal (LLN) being 12.1 g/dL, in two female healthy volunteers receiving BLS-11 followed by Tecfidera. All of these individuals had normal serum hemoglobin values at follow-up.

Nine healthy volunteers exhibited temporary decreases in hematocrit (from normal at Day –1 of Period 1 to below lower limit of reference range normal on Day 2 of Period 2, including five subjects receiving BLS-11 followed by Tecfidera and four subjects receiving Tecfidera followed by BLS-11. The lowest post-dose value noted was 33.2% (LLN: 35.0%) in a female subject receiving Tecfidera followed by BLS-11. All of these individuals had normal hematocrit values at follow-up.

Reviewer Comment: Analysis of laboratory values following chronic Tecfidera exposure in patients with MS and psoriasis have demonstrated small decreases in hemoglobin (approximately 2 g/dL) and hematocrit (on average less than 1% from baseline) serum values. The mechanism for these changes is unclear, and the decreases become smaller in magnitude as duration of Tecfidera exposure increases. The observations in the BLS-11 studies are within the expected shift associated with chronic exposure. The rectification of these values to normal reference range at follow-up appears to confirm a relationship to BLS-11 exposure and reassures that the effect is not permanent.

8.4.6. Vital Signs

There were no significant differences from baseline in pulse rate, systolic blood pressure, or diastolic blood pressure in subjects exposed to BLS-11 as compared to healthy volunteers exposed to Tecfidera. There were no notable trends in vital sign values or mean change from baseline in vital sign values when analyzed by age, sex, or race subgroups

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Table 21: Applicant Table, Pre- and Post-Dose Pulse Rates, All Studies

Vital Sign	MMF 190 mg Fasted (N=89)	MMF 190 mg Fed (N=39)	MMF 200 mg Fasted (N=50)	MMF Combined [1] (N=178)	Tecfidera 240 mg (N=99)
Pulse Rate (beats/min)					
Baseline					
N	89	39	50	178	99
Mean	70	72	70	70	69
SD	12.7	13.5	11.1	12.4	10.8
Median	68	69	72	69	69
Min, Max	39, 140	57, 137	46, 116	39, 140	43, 119
2 Hours Post-Dose					
N	89	39	50	178	99
Mean	69	76	69	71	72
SD	10.9	11.4	8.8	10.8	13.9
Median	68	75	69	69	70
Min, Max	49, 98	60, 118	50, 88	49, 118	46, 142
Change from Baseline to 2 Hours Post-Dose					
N	89	39	50	178	99
Mean	0	4	-2	0	2
SD	11.2	9.4	7.6	10.1	14.5
Median	-1	5	-1	0	-1
Min, Max	-55, 52	-19, 24	-28, 16	-55, 52	-19, 73
Pulse Rate (beats/min)					
24 Hours Post-Dose					
N	88	39	50	177	99
Mean	72	76	75	74	72
SD	12.2	12.7	10.8	12.0	10.5
Median	71	74	75	73	72
Min, Max	33, 114	52, 125	50, 115	33, 125	42, 106
Change from Baseline to 24 Hours Post-Dose					
N	88	39	50	177	99
Mean	2	4	5	3	2
SD	11.3	11.2	6.5	10.1	7.9
Median	3	3	5	3	3
Min, Max	-62, 28	-21, 31	-6, 20	-62, 31	-15, 37

Table 22: Applicant Tables, Pre- and Post-Dose Systolic Blood Pressures, All Studies

Vital Sign	MMF 190 mg Fasted (N=89)	MMF 190 mg Fed (N=39)	MMF 200 mg Fasted (N=50)	MMF Combined [1] (N=178)	Tecfidera 240 mg (N=99)
Systolic Blood Pressure (mmHg)					
Baseline					
N	89	39	50	178	99
Mean	116	115	119	117	116
SD	12.0	14.5	13.0	12.9	13.0
Median	116	114	118	116	116
Min, Max	90, 143	91, 148	98, 169	90, 169	64, 156
2 Hours Post-Dose					
N	89	39	50	178	99
Mean	116	110	120	116	120
SD	12.4	10.4	12.7	12.6	13.2
Median	114	110	120	114	118
Min, Max	91, 146	91, 132	94, 154	91, 154	91, 149
Change from Baseline to 2 Hours Post-Dose					
N	89	39	50	178	99
Mean	-1	-5	1	-1	3
SD	10.3	9.2	10.1	10.2	13.7
Median	-2	-3	1	-2	2
Min, Max	-33, 35	-30, 12	-22, 27	-33, 35	-21, 82

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Systolic Blood Pressure (mmHg)

24 Hours Post-Dose					
N	88	39	50	177	99
Mean	119	113	119	118	122
SD	13.1	13.8	12.9	13.4	14.8
Median	118	112	119	117	121
Min, Max	91, 164	90, 135	95, 146	90, 164	90, 180

Change from Baseline to 24 Hours Post-Dose					
N	88	39	50	177	99
Mean	3	-2	0	1	5
SD	11.9	9.3	11.1	11.2	14.3
Median	2	-2	-1	1	4
Min, Max	-24, 51	-23, 20	-27, 28	-27, 51	-31, 59

Test Time	Statistic	Treat A	Treat B	OVERALL

Screening	N			16
	Mean			125.2
	SD			8.3
	Median			124.0
	Max			139.0
	Min			106.0
P1 Pre-dose	N	8	8	
	Mean	125.8	120.8	
	SD	9.1	7.2	
	Median	128.5	122.5	
	Max	139.0	132.0	
	Min	113.0	110.0	
P1 2 hours Post-dose	N	8	8	
	Mean	117.5	115.1	
	SD	11.4	7.6	
	Median	115.5	114.0	
	Max	140.0	128.0	
	Min	105.0	105.0	
P1 5 hours Post-dose	N	8	8	
	Mean	120.0	119.6	
	SD	7.1	10.7	
	Median	121.5	119.0	

Treatment A: 1 × 95 mg Monomethyl Fumarate Delayed-Release Capsule
Treatment B: 2 × 95 mg Monomethyl Fumarate Delayed-Release Capsules

Test Time	Statistic	Treat A	Treat B	OVERALL

	Max	128.0	137.0	
	Min	106.0	104.0	
P1 12 hours Post-dose	N	8	8	
	Mean	112.5	116.1	
	SD	9.4	9.2	
	Median	109.5	116.0	
	Max	130.0	132.0	
	Min	102.0	100.0	
P1 24 hours Post-dose	N	8	8	
	Mean	113.3	114.9	
	SD	9.1	12.9	
	Median	114.5	115.0	
	Max	127.0	134.0	
	Min	95.0	95.0	
P2 Pre-dose	N	8	8	
	Mean	121.5	119.3	
	SD	12.8	11.8	
	Median	123.0	119.5	
	Max	137.0	136.0	
	Min	98.0	100.0	
P2 2 hours Post-dose	N	8	8	

Treatment A: 1 × 95 mg Monomethyl Fumarate Delayed-Release Capsule
Treatment B: 2 × 95 mg Monomethyl Fumarate Delayed-Release Capsules

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Table 23: Applicant Table, Pre- and Post-Dose Diastolic Blood Pressures, All Studies

Vital Sign	MMF 190 mg Fasted (N=89)	MMF 190 mg Fed (N=39)	MMF 200 mg Fasted (N=50)	MMF Combined [1] (N=178)	Tecfidera 240 mg (N=99)
Diastolic Blood Pressure (mmHg)					
Baseline					
N	89	39	50	178	99
Mean	74	74	74	74	73
SD	8.5	9.8	10.2	9.2	9.7
Median	75	75	73	75	73
Min, Max	57, 93	45, 87	50, 94	45, 94	40, 93
2 Hours Post-Dose					
N	89	39	50	178	99
Mean	75	71	74	74	74
SD	9.0	7.6	9.4	8.9	10.4
Median	74	71	73	74	74
Min, Max	53, 95	55, 87	47, 102	47, 102	50, 96
Change from Baseline to 2 Hours Post-Dose					
N	89	39	50	178	99
Mean	1	-3	0	0	0
SD	6.8	5.8	8.7	7.4	9.7
Median	1	-3	-1	-1	0
Min, Max	-21, 20	-18, 10	-12, 31	-21, 31	-24, 46
Diastolic Blood Pressure (mmHg)					
24 Hours Post-Dose					
N	88	39	50	177	99
Mean	76	73	73	74	75
SD	10.9	9.9	10.3	10.6	10.4
Median	75	73	73	73	74
Min, Max	53, 142	52, 93	50, 96	50, 142	51, 100
Change from Baseline to 24 Hours Post-Dose					
N	88	39	50	177	99
Mean	2	-2	-1	0	1
SD	11.2	6.0	9.1	9.8	9.9
Median	1	-3	0	0	1
Min, Max	-16, 76	-15, 10	-30, 31	-30, 76	-25, 40
Test Time	Statistic	Treat A	Treat B	OVERALL	
Screening	N			16	
	Mean			77.7	
	SD			9.6	
	Median			76.0	
	Max			96.0	
	Min			61.0	
P1 Pre-dose	N	8	8		
	Mean	72.6	77.5		
	SD	9.5	8.5		
	Median	72.0	78.0		
	Max	84.0	89.0		
	Min	57.0	66.0		
P1 2 hours Post-dose	N	8	8		
	Mean	74.6	74.4		
	SD	7.4	5.6		
	Median	75.0	72.5		
	Max	86.0	82.0		
	Min	63.0	68.0		
P1 5 hours Post-dose	N	8	8		
	Mean	76.1	76.3		
	SD	6.9	10.0		
	Median	75.5	74.0		

Treatment A: 1 × 95 mg Monomethyl Fumarate Delayed-Release Capsule
Treatment B: 2 × 95 mg Monomethyl Fumarate Delayed-Release Capsules

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Test Time	Statistic	Treat A	Treat B	OVERALL
	Max	86.0	89.0	
	Min	67.0	64.0	
P1 12 hours Post-dose	N	8	8	
	Mean	74.3	75.1	
	SD	6.3	9.0	
	Median	75.5	74.0	
	Max	82.0	88.0	
	Min	63.0	64.0	
P1 24 hours Post-dose	N	8	8	
	Mean	72.9	74.3	
	SD	5.5	8.7	
	Median	75.5	72.0	
	Max	77.0	85.0	
	Min	61.0	65.0	
P2 Pre-dose	N	8	8	
	Mean	75.4	71.6	
	SD	7.4	10.2	
	Median	76.0	69.5	
	Max	87.0	89.0	
	Min	65.0	59.0	
P2 2 hours Post-dose	N	8	8	

Treatment A: 1 × 95 mg Monomethyl Fumarate Delayed-Release Capsule
Treatment B: 2 × 95 mg Monomethyl Fumarate Delayed-Release Capsules

Source: Integrated Safety Summary, pages 339-360 and Study Report BLS-11-108 pages 92-97

Reviewer Comment: There are no significant changes from baseline in pulse rates or blood pressure readings noted in any group.

8.4.7. Electrocardiograms (ECGs)

The applicant obtained single 12-lead electrocardiograms (ECGs) at screening and 2 hours prior to dosing in Period 1. Mean ECG parameters for heart rate, PR, QRS, QT, and QTcF remained within normal limits for all time points between both treatments.

There were no AEs associated with vital signs or ECG abnormalities in this study.

One healthy volunteer, who was to receive BLS-11 followed by Tecfidera, exhibited a QTcF interval of 454 msec at the screening visit; the QTcF value then decreased to 445 msec at the pre-dose of Period 1. This individual had no other individual QTcF intervals > 450 msec at any of the recorded time points. No other volunteers had QTcF intervals > 450 msec at any recorded time point.

Reviewer Comment: The presence of a mildly prolonged QTcF interval at screening is not a consequence of exposure to study drug.

One subject experienced TEAE of palpitations in this study. The healthy volunteer was a 37-year-old female (receiving Tecfidera followed by BLS-11) who reported the AE of mild palpitations ("heart flutter episodes") that began approximately 2.3 days after dosing with BLS-

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11. The volunteer indicated that the symptom occurred intermittently, lasting between 15 minutes and 3 hours in duration. The volunteer reported mild anxiety at the same time as the palpitations. Vital signs taken at the time the subject reported the symptoms showed a BP of 117/68 mm Hg and pulse rate of 68 bpm. An ECG taken at the time of the report was normal. The TEAE resolved after 9.6 days. The investigator considered TEAEs of palpitations and anxiety to be possibly related to the study drug.

Reviewer Comment: The likelihood of palpitations and cardiac awareness more than two days post-treatment being attributable to a single dose of BLS-11 is very unlikely given that serum MMF levels would be below the limits of detection at this time point. The volunteer's acknowledged anxiety is a more likely etiology.

8.4.8. QT

Not applicable. A QT study was not required for this application.

8.4.9. Immunogenicity

Not applicable.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Gastrointestinal Tolerability

The listed drug for this application, Tecfidera, causes gastrointestinal symptoms such as nausea and abdominal pain. The applicant examined these symptoms and defined "gastrointestinal tolerability" as all TEAEs pertaining to nausea, vomiting, diarrhea, constipation, and abdominal pain. Specific MedDRA coded terms were included in these individual evaluations. These terms included abdominal pain (abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness, abdominal distension, abdominal discomfort and suprapubic pain); nausea; vomiting; constipation; and diarrhea (diarrhea and flatulence). If a patient experienced the same event more than once after a treatment, the incidence was noted only once. Only events noted within a timeframe deemed reasonable by the PI for an association with the treatment are included, and applying these criteria only removed 2 events total from the TEAE Gastrointestinal Events. Using these criteria, across all studies, 23 of 354 (6%) of exposed patients treated with any formulation of BLS-11 reported gastrointestinal tolerability events compared with 11 of 147 (7%) of all Tecfidera-treated subjects. The presence of a high-fat content meal before administration resulted in a higher percentage of reports of Gastrointestinal Disorders AEs. Following a pre-dose high-fat meal, 5 of 39 (13%) subjects

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reported gastrointestinal AEs at the 190 mg BLS-11 dose, compared to 3 out of 105 (4%) when those same subjects were fasted prior to receiving 190 mg of BLS-11.

Table 24: Reviewer Table, All Gastrointestinal Tolerability Adverse Events, All Studies, All Patients

SYSTEM ORGAN CLASSIFICATION Preferred Term	BLS-11 95 mg Fasted (n=16)	BLS-11 190 mg Fasted (n=105)	BLS-11 190 mg Fed (n=39)	BLS-11 200 mg Fasted (n=98)	BLS-11 214 mg Fed (n=96)	BLS-11 All (n=354)	Tecfidera 240 mg (n=147)
Any GI Tolerability Event	1 (6%)	3 (3%)	5 (13%)	9 (9%)	5 (5%)	23 (6%)	11 (7%)
Abdominal Pain*	1 (6%)	2 (2%)	3 (8%)	5 (5%)	1 (1%)	12 (3%)	5 (3%)
Abdominal pain	1 (6%)	1 (1%)	0	1 (1%)	1 (1%)	4 (1%)	2 (1%)
Abdominal pain upper	0	0	1 (3%)	2 (2%)	0	3 (1%)	2 (1%)
Abdominal discomfort	0	1 (1%)	1 (3%)	0	0	2 (1%)	1 (1%)
Abdominal distension	0	0	1 (3%)	1 (1%)	0	2 (1%)	2 (1%)
Abdominal pain lower	0	0	0	1 (1%)	0	1 (1%)	0
Abdominal tenderness	0	0	0	1 (1%)	0	1 (1%)	0
Suprapubic pain	0	0	0	1 (1%)	0	1 (1%)	0
Constipation	0	0	2 (5%)	0	0	2 (1%)	0
Diarrhea**	1 (6%)	1 (1%)	0	1 (1%)	1 (1%)	4 (1%)	6 (4%)
Diarrhea	1 (6%)	1 (1%)	0	1 (1%)	1 (1%)	4 (1%)	5 (3%)
Flatulence	0	0	0	0	0	0	1 (1%)
Nausea/Vomiting***	0	0	2 (5%)	3 (3%)	5 (5%)	10 (3%)	5 (3%)
Nausea	0	0	1 (3%)	3 (3%)	3 (3%)	7 (2%)	5 (3%)
Vomiting	0	0	1 (3%)	0	2 (2%)	3 (1%)	0

Source: Summary of Clinical Safety, Table 3-7, page 54, revised ISS Table 5.1.1. received October 26, 2018

* includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, abdominal distension, and suprapubic pain

** includes diarrhea and flatulence

*** includes nausea and vomiting

Reviewer Comment: The observation of more gastrointestinal symptoms in the fed versus fasted conditions (13% versus 6%, 3%, and 9%) might suggest that the recommendation of taking BL-11 with or without food is not entirely supported by the submitted studies' data. However, in the pivotal trial data of the listed drug, Tecfidera, patients reported less frequent nausea (8% vs. 3%) and vomiting (6% vs. 0%), and despite this observed disparity, the current labeling for Tecfidera specifies it may be taken "with

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and without food.” Given the known discrepancy in symptoms with the listed drug, the similar overall observed incidence rates (7% versus 9%) of GI symptoms related to administration between BLS-11 and the listed drug, Tecfidera, and the overall mild severity of the reported events, it therefore is acceptable to make the same recommendation for BLS-11 despite the disparate incidence rate of symptoms noted in the fed state. It may become clear with administration to a larger population that BLS-11 causes significantly more GI distress with than without food, but the small exposure numbers and absence of any chronic dosing experience preclude that conclusion at this time.

8.5.2. White Blood Cell Count

Given the known effect of chronic exposure to the listed drug on serum white blood cell (WBC) counts, the applicant included an analysis of pre- and post-exposure white blood cell counts that is included below. The applicant reported no observed effect on white blood counts in any treatment condition. There were no notable trends in change from baseline in WBC counts when analyzed by age, sex, or race subgroups

Table 25: Reviewer Table, Pre- and Post-Dose White Blood Cell Counts, Studies BLS-11-103, 104, 105, 106, and 108

Hematology Leukocytes ($\times 10^3/\mu\text{L}$)	BLS-11 All Doses*	Tecfidera 240 mg
Baseline		
N	88	49
Mean	6.8	7.0
SD	1.85	1.66
Median	6.7	6.8
Min, Max	3.6, 14.1	4.5, 10.6
Post-Treatment (at least ≥ 2 days after treatment)		
N	88	49
Mean	6.0	5.9
SD	1.31	1.41
Median	6.1	5.8
Min, Max	3.1, 9.9	3.5, 8.7
Change from Baseline Value to Post-Treatment		
N	88	49
Mean	-0.8	-1.1
SD	1.66	1.25

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Median	-0.6	-1.2
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Source: Summary of Clinical Safety, Table 3-8, page 56 and Study Report BLS-11-108, pages 144 and 151

*includes all patients with baseline and post-treatment dose complete blood counts available from the included studies.

Reviewer Comment: There were no noteworthy changes from baseline in any of the obtained laboratory values. The leukocyte mean changes are within the boundaries of what would be expected to occur in any healthy individual with serial testing. A single dose of BLS-11 should not appreciably change the white blood cell count. Six months of daily Tecfidera exposure is associated with a decline in serum white blood cell count of approximately 30%; the mechanism of this decrease is not known.¹⁰ Acute exposure to Tecfidera, or to BLS-11, would not be expected to replicate this chronic dosing effect on the white blood cell count.

8.6. Safety Analyses by Demographic Subgroups

Age

The applicant analyzed age in two groups, patients < 37 years of age as of date of treatment with BLS-11, and age ≥ 37 years old as of date of treatment with BLS-11. When frequency of TEAEs was analyzed by these age subgroups, the percentages of volunteers with at least one reported TEAE were generally similar for subjects < 37 years of age after treatment with BLS-11 (range of 63%-72% across the three individual BLS-11 groups) compared with the Tecfidera group (61%). This was also true for subjects aged ≥ 37 years following treatment with BLS-11 (range of 55% to 63% across the 3 individual BLS-11 groups) compared with the Tecfidera group (56%).

Treatment-emergent AEs within the Gastrointestinal Disorders SOC tended to occur in a larger percentage of volunteers < 37 years of age following dosing with BLS-11 190 mg under fed conditions and BLS-11 200 mg under fasted conditions (22% following either of the studied doses) compared with the Tecfidera group (9%). For volunteers ≥ 37 years of age, TEAEs within the Gastrointestinal Disorders SOC tended to occur in a higher percentage of individuals following treatment with Tecfidera (11%) compared with BLS-11 (range of 0% to 5% across the individual BLS-11 groups).

Flushing occurred after 55 of the 90 BLS-11 acute exposures (61%) compared with 52% for Tecfidera in volunteers < 37 years of age and after 43 of the 88 BLS-11 subject exposures (49%) in those ≥ 37 years of age compared with 49% following treatment with Tecfidera.

Reviewer Comment: The small differences in symptoms between age groups do not

appear significant and are difficult to interpret given the relatively small number of subject exposures.

Sex

The applicant analyzed TEAEs in the male and female subgroups. When the applicant analyzed the frequency of TEAEs by gender, the percentages of subjects with at least one TEAE were higher for female healthy volunteers (range of 67%-73% across all three trials of different BLS-11 doses and 68% in the Tecfidera group) compared with male subjects (range of 54% to 65% across the BLS-11 trials and 51% in the Tecfidera group). Percentages of subjects with at least one reported TEAE were similar across the BLS-11 dose groups compared with the Tecfidera group within both the male and female subgroups, with at least one TEAE noted following 60 of the 87 BLS-11 subject exposures (69%) for female subjects and after 52 of 91 exposures (57%) for male subjects. Flushing occurred after 53 of the 87 BLS-11 subject exposures (61%) in female subjects and after 45 of the 91 BLS-11 subject exposures (49%) in male subjects, compared with 47% and 55% of male subjects and female subjects, respectively, following treatment with Tecfidera.

Treatment-emergent AEs of Gastrointestinal Disorders SOC occurred in up to 23% of female subjects following BLS-11 exposure and in 23% of volunteers exposed to Tecfidera. The only TEAE within the Gastrointestinal Disorders SOC occurring in male subjects was diarrhea, which occurred in 1 of 54 male subjects (2%) after dosing with BLS-11 190 mg under fasted conditions. For the Tecfidera group, TEAEs within this SOC occurred exclusively in female subjects.

Higher percentages of male and female volunteers treated with BLS-11 experienced at least one TEAE within the Nervous System Disorders SOC compared with the Tecfidera group. The TEAEs following BLS-11 exposures were of mild or moderate severity and resolved quickly. Headaches were noted in three male subjects, and somnolence, tremor, and presyncope, occurred in one male subject apiece. All of these TEAEs were mild severity with one exception, a headache that was of moderate severity. All Nervous System Disorders SOC events resolved within 1 day of onset except for an adverse event of somnolence that resolved 2 days after onset. For female subjects receiving BLS-11 200 mg, TEAEs were headache occurring in 2 female subjects and dizziness and presyncope occurring in 1 subject each. All of these TEAEs were of moderate severity except for the event of dizziness, which was rated as mild severity, and all resolved within 1 day of onset except for a lone instance of headache that resolved 3 days after onset. One male and one female subject in the Tecfidera group experienced a TEAE within this SOC. Both were headaches of TEAEs of moderate severity, and both resolved one-day after onset.

Reviewer Comment: The increased frequency of events in women is of concern because the intended population is patients with multiple sclerosis, which is overwhelmingly female. However, the observed events are expected based on prior experience with Tecfidera, and the observed incidences of the TEAEs associated with BLS-11 are similar to those reported for women exposed to the listed drug.

Race

The applicant reports that the percentages of subjects experiencing at least one TEAE following dosing with BLS-11 were broadly similar to the percentages observed following dosing with Tecfidera for both Caucasian and non-Caucasian subjects. Across 150 Caucasian individuals exposed to BLS-11, TEAEs occurred in 98 Caucasian subject exposures (65%) compared with 47 of 82 Caucasian subjects (57%) treated with Tecfidera. Considering all 28 BLS-11 non-Caucasian subject exposures, TEAEs occurred in 14 out of 28 non-Caucasian subject exposures to Tecfidera (50%) compared with 47 of the 82 Caucasian subjects (57%) treated with Tecfidera.

Treatment-emergent AEs within the Gastrointestinal Disorders SOC and the Neurological Disorders SOC did not differ within the Caucasian subgroup following dosing with BLS-11 when compared to Caucasian volunteers exposed to Tecfidera.

For the non-Caucasian subgroup exposed to Tecfidera, there were two subjects who reported Gastrointestinal Disorders and no subjects who reported Nervous System Disorders. Across the 28 BLS-11 non-Caucasian subject exposures, at least one TEAE within the Gastrointestinal Disorders and Nervous Systems Disorders SOCs occurred after three and 4 BLS-11 subject exposures, respectively.

Reviewer Comment: There do not appear to be large differences in symptoms reported by Caucasian and non-Caucasian volunteers exposed to BLS-11. The small number of acute exposures precludes any definitive statements about minor discrepancies observed between these broad, heterogeneous racial categories.

8.7. Specific Safety Studies/Clinical Trials

Not applicable. As a 505(b)(2) pathway submission, this NDA derives its safety database support from the application for the listed drug, Tecfidera.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Not applicable.

8.8.2. Human Reproduction and Pregnancy

Not applicable.

8.8.3. Pediatrics and Assessment of Effects on Growth

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Not applicable.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Not applicable. Bafiertam is not currently marketed anywhere in the world; no postmarketing safety experience is available for review.

8.9.2. Expectations on Safety in the Postmarket Setting

The expectations regarding safety are that the safety profile of BLS-11 will be identical to that of the listed drug, Tecfidera.

8.9.3. Additional Safety Issues From Other Disciplines

No other safety issues were communicated at the time of submission of this review.

8.10. Integrated Assessment of Safety

9. Advisory Committee Meeting and Other External Consultations

Not applicable.

10. Labeling Recommendations

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10.1. Prescription Drug Labeling

The labeling has not been finalized at the time of this review.

The expectation is that the approved labeling will be essentially identical to the approved labeling for the listed drug, Tecfidera.

All safety-related sections will be reviewed and edited to comply with Agency labeling formats.

10.2. Nonprescription Drug Labeling

Not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

A REMS is not required for the safe use of Bafiertam in adult patients with RMS. There are no new identified safety issues where a REMS would be expected to mitigate identified risks. Tecfidera, the listed drug, did not have a REMS at the time of its approval in March 2013.

12. Postmarketing Requirements and Commitments

When the listed drug, Tecfidera, was approved in March 2013, FDA issued several postmarketing requirements including several nonclinical studies regarding abuse potential. The only clinical study required was a large, long-term prospective observational study in adult patients with RMS “to determine the nature and incidence of serious infections including opportunistic infections...” While acquiring data for this required postmarketing study, postmarketing experience with Tecfidera revealed that, a small number of patients with persistent lymphopenia developed a serious neurological complication due to re-activation of a latent virus, progressive multifocal leukoencephalopathy (PML). The occurrences of PML led to labeling changes for Tecfidera.

Other postmarketing requirements such as a pregnancy registry are still under consideration at the time of this review.

Reviewer Comment: A requirement for a longitudinal study of opportunistic infections associated with Bafiertam is not necessary as a postmarketing obligation. This application establishes bioequivalence of Bafiertam to the listed drug. The safety risks of BLS-11, including PML, should be approximately equal to those associated with DMF. Furthermore,

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after five years of postmarketing experience, the risks associated with the listed drug are well characterized and can inform labeling of this product now and in the future. A risk of PML must be included on Bafiertam labeling despite no observed occurrences in the submitted studies because the studies in this NDA are single administration Phase 1 studies, and PML risk is associated with prolonged lymphopenia following several months of exposure to the therapy.

13. Appendices

13.1. References

1. Kurtzke JF. On the evaluation of disability in multiple sclerosis. *Neurology*. 1961;11:686-694.
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3. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol*. 2011;69(2):292-302.
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8. Paz Soldan MM, Novotna M, Abou Zeid N, et al. Relapses and disability accumulation in progressive multiple sclerosis. *Neurology*. 2015;84(1):81-88.
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10. Khatri BO, Garland J, Berger J, et al. The effect of dimethyl fumarate (Tecfidera) on lymphocyte counts: A potential contributor to progressive multifocal leukoencephalopathy risk. *Multiple sclerosis and related disorders*. 2015;4(4):377-379.

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13.2. Financial Disclosure

There were no relevant financial disclosures on Form FDA 3455 for any study submitted with NDA 210296. None of the individuals listed as investigators on the list of investigators provided by the applicant was an employee of Banner Pharmaceuticals.

Covered Clinical Study (Name and/or Number): BLS-11-101, BLS-11-102, BLS-11-103, BLS-11-104, BLS-11-105, and BLS-11-106

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>36</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>N/A</u> Significant payments of other sorts: <u>N/A</u> Proprietary interest in the product tested held by investigator: <u>N/A</u> Significant equity interest held by investigator in S Sponsor of covered study: <u>N/A</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>N/A</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PAUL R LEE
11/07/2018