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APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA or BLA Number	210296
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Submission Date	1/18/2018
Submission Type	505(b)(2) NDA
Brand Name	BAFIERTAM™
Generic Name	Monomethyl Fumarate
Dosage Form and Strength	Delayed Release Capsule (95 mg)
Route of Administration	Oral
Proposed Indication	For the treatment of patients with relapsing forms of multiple sclerosis
Applicant	Banner Life Sciences
OCP Review Team	Jagan Mohan Parepally, Ph.D., Angela Men, M.D., Ph.D.

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1. EXECUTIVE SUMMARY

This is a 505(b)(2) New Drug Application (NDA) to support the marketing approval of Bafiertam ™ (monomethyl fumerate, MMF) for the treatment of relapsing forms of Multiple Sclerosis (MS) using Tecfidera® (dimethyl fumarate) delayed-release capsules, 240 mg as the listed drug (LD). Dimethyl fumarate undergoes rapid presystemic hydrolysis by esterases and is converted to its active metabolite, MMF. Dimethyl fumarate is not quantifiable in plasma following oral administration. In this NDA, the Applicant submitted the summary and literature review provided to conclude that there exists no large and compelling body of literature either confirming or refuting the hypothesis that chronic administration of MMF causes substantially different transcriptional, antioxidant, or cellular effects than those observed in association with DMF. There is no clear clinical implication that any observed nonclinical differences between MMF and DMF will yield significant clinical differences in the effectiveness of MMF as compared to Tecfidera® in the treatment of relapsing MS. The sponsor is relying on bioequivalence (BE) of MMF to bridge the FDA's finding of safety and effectiveness for Tecfidera® Delayed-Release Capsules and is seeking the same indication approved for Tecfidera.

The sponsor has developed Bafiertam, a soft gelatin delayed-release capsule for oral administration, containing 95 mg of monomethyl fumarate. The proposed starting dose is 95 mg twice a day, for 7 days followed by a maintenance dose of 190 mg twice a day.

The clinical development program included five Phase 1 PK studies using the final capsule formulation. These studies include a pivotal bioequivalence study to compare BLS-11 ((b) (4) formulation) and Tecfidera, food-effect study and dose proportionality. The applicant demonstrated bioequivalence (BE) of MMF exposure following administration of two 95 mg Bafiertam delayed release capsules and one Tecfidera® 240 mg DMF delayed release capsule in a pivotal bioequivalence study.

A consult was sent to the Office of Scientific Inspections and Surveillance (OSIS) requesting clinical and bioanalytical site inspections for pivotal relative bioavailability study BLS-11-104. OSIS concluded that the data are acceptable based on the records of recent inspections of these clinical and bioanalytical sites.

1.1 Recommendations

The office of Clinical Pharmacology (OCP) has reviewed the information contained in NDA 210296 and supports the approval of Bafiertam™ for the treatment of relapsing forms of multiple sclerosis. Key review issues with specific recommendations and comments are summarized below:

Review Issue	Recommendations and Comments

Pivotal or supportive evidence of effectiveness and safety	The exposures and pharmacokinetic profiles of MMF following administration of 190 mg Bafiertam™ and Tecfidera® 240 mg were bioequivalent; therefore, the pharmacokinetic bridge was established to support evidence of effectiveness and safety form LD, Tecfidera.
General dosing instructions	The dosing recommendations are based on LD and the established pharmacokinetic bridge. Initial titration with a starting dose of 95 mg twice a day for 7 days is recommended, followed by a the dose should be increased to the maintenance dose of 190 mg (two 95 mg capsules) twice a day orally with or without food.
Dosing in patient subgroups (intrinsic and extrinsic factors)	No therapeutic individualization is necessary for extrinsic/intrinsic factors and patient subgroups based on LD, Tecfidera.
Labeling	General dosing recommendations are acceptable. These recommendations are similar to that approved for Tecfidera. Bafiertam can be administered with or without food.
Bridge between the to-be-marketed and clinical trial formulations	The to-be-marketed formulation was used in the pivotal BE study.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Dimethyl fumarate, pro-drug of monomethyl fumarate is indicated for the treatment of relapsing forms of MS. DMF undergoes rapid presystemic hydrolysis by esterases and is converted to its active metabolite, MMF. Dimethyl fumarate is not quantifiable in plasma following oral administration. Monomethyl fumarate has been shown to activate the Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway in vitro and in vivo in animals and humans. The Nrf2 pathway is involved in the cellular response to oxidative stress. Monomethyl fumarate has been identified as a nicotinic acid receptor agonist in vitro. However, the mechanism by which monomethyl fumarate exerts its therapeutic effect in multiple sclerosis is unknown.

The applicant demonstrated bioequivalence (BE) of MMF exposure following administration of two 95 mg MMF delayed release capsules and one 240 mg DMF delayed release capsule. The effect of food was also evaluated. See section 3.3 for further details.

2.1.1 Pharmacokinetic Comparison of MMF between Bafiertam and Tecfidera

Monomethyl fumerate exposure (Cmax and AUCs) following Bafiertam 190 mg was bioequivalent to Tecfidera 240 mg under fasting conditions (Figures and forest plots below). The median time to maximum concentration (Tmax) was about 4 hours and 2.5 after administration of Bafiertam 190 mg and Tecfidera 240 mg respectively. However, the Tmax range was essentially similar for both products. The elimination half-life of MMF was about 0.57 hours following Bafiertam 190 mg which was similar to Tecfidera 240 mg.

2.1.2 Effect of Food on the Pharmacokinetics of Monomethyl Fumarate

High fat meal delayed the median Tmax of MMF from 4.0 and 10.75 hours and decreased the peak plasma concentration of MMF by approximately 20% following administration of a single dose of BLS-11 190 mg. However, there was no significant food effect on AUC of MMF. Food

may reduce the incidence of flushing for Tecfidera. However, the incidence of flushing was unaffected in these single dose Bafiertam studies. The exposure response relationship for MMF is unknown, this food effect finding is similar to the LD, TECFIDERA, (decreased Cmax by 40% and delayed Tmax from 2 hours to 5.5 hours). Monomethyl fumarate is indicated for chronic administration. Therefore, BAFIERTAM could be administered with or without food.

2.1.3 Effect of Food on the Pharmacokinetics of Monomethyl Fumarate

Dose proportionality of MMF was demonstrated following single-dose administration of 1 x 95 mg and 2 x 95 mg Monomethyl Fumarate 95 mg Delayed Release Capsules in healthy subjects (Study BLS-11-108). The PK parameters of MMF were found to be essentially dose proportional.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The dosing recommendations are based on LD and the established pharmacokinetic bridge. Initial titration with a starting dose of 95 mg twice a day for 7 days is recommended, followed by the dose increased to the maintenance dose of 190 mg (two 95 mg capsules) twice a day orally with or without food.

2.2.2 Therapeutic individualization

No therapeutic individualization is necessary for extrinsic/intrinsic factors based on LD, Tecfidera.

2.4 Summary of Labeling Recommendations

General dosing recommendations are acceptable. These recommendations are similar to that approved for Tecfidera. Bafiertam can be administered with or without food similar to labeling recommendations for LD.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

The applicant (Banner Life Sciences, Inc) has developed Delayed Release (DR) capsules, 95 mg and is seeking approval for use for the treatment of MS. The drug product is a soft gelatin delayed-release capsule for oral administration, containing 95 mg of monomethyl fumarate consisting of the following inactive ingredients: Glyceryl caprylate/caprate; povidone; polyoxyl hydrogenated castor oil; and lactic acid.

Dimethyl fumarate undergoes rapid presystemic hydrolysis by esterases and is converted to its active metabolite, MMF. Dimethyl fumarate is not quantifiable in plasma following oral administration. In this NDA, to support the hypothesis that there may be clinical effects of DMF that are not attributable to its metabolite MMF as part of the consideration of a 505(b)(2)

application for MMF. From the summary and literature review provided it was concluded that there exists no large and compelling body of literature either confirming or refuting the hypothesis that chronic administration of MMF causes substantially different transcriptional, antioxidant, or cellular effects than those observed in association with DMF. There is no clear clinical implication that any observed nonclinical differences between MMF and DMF will yield significant clinical differences in the effectiveness of MMF as compared to Tecfidera® in the treatment of relapsing MS.

The Sponsor conducted 5 Phase 1 studies including bioequivalence, food effect and dose proportionality studies in healthy volunteers.

3.2 General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	Monomethyl fumarate has been shown to activate the Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway in vitro and in vivo in animals and humans. The Nrf2 pathway is involved in the cellular response to oxidative stress. Monomethyl fumarate has been identified as a nicotinic acid receptor agonist in vitro. However, the mechanism by which monomethyl fumarate exerts its therapeutic effect in multiple sclerosis is unknown.
General Information	
Bioanalysis	Plasma MMF concentrations were measured by a validated liquid chromatographic-tandem mass spectrometric (LC/MS/MS) bioanalytical methods. Monomethyl Fumarate-d5 was used as the internal standard. The lower limit of quantitation was 25 ng/mL.
Healthy Volunteers vs Patients	All the studies were conducted in healthy subjects.
Dose Proportionality	The PK parameters of MMF following administration of a single and two capsules of the final dosage form were found to be essentially dose proportional (Study BLS-11-108).
ADME	
Absorption	Median time to maximum concentration (Tmax) following oral administration of BAFIERTAM 190 mg (two 95 mg monomethyl fumarate delayed-release capsules) under fasting conditions of monomethyl fumarate was 4.03 hours. Food Effect: High fat meal delayed the Tmax of MMF by 3.25 and 6.75 hours in two different studies and decreased the peak plasma concentration of MMF by 20 to 30% following administration of a single dose of BLS-11 190 mg. However, there was no significant food effect on AUC of MMF.
Distribution	The estimated volume of distribution of monomethyl fumarate varies between 53 and 73 L in healthy subjects. Human plasma protein binding of monomethyl fumarate is 27-45% and independent of concentration.

Metabolism	Monomethyl fumarate is metabolized through the tricarboxylic acid (TCA) cycle, with no involvement of the cytochrome P450 (CYP450) system. Fumaric and citric acid, and glucose are the major metabolites of monomethyl fumarate in plasma.
Elimination	Major route of elimination of MMF is conversion to CO_2 and exhalation. Renal and fecal elimination are minor routes of elimination for monomethyl fumarate. Trace amounts of unchanged monomethyl were present in urine.

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

This is a 505(b)(2) application for Bafiertam (MMF) using Tecfidera (DMF) as the listed drug (LD). This application relies on the efficacy and safety data that formed the basis for approval of Tecfidera. As DMF undergoes rapid presystemic hydrolysis by esterases and is converted to its active metabolite, MMF, and DMF is not quantitatively measurable, the development program utilized a PK of MMF comparability approach to bridge efficacy and safety to Tecfidera®.

Two bioequivalence studies (BLS-11-103 and BLS-11-104) were conducted to compare BLS-11 ([(b) (4)] based formulation containing two different dose strengths) and Tecfidera/DMF and to aid the final MMF dose selection. Both studies were randomized crossover in design with at least 4 days between the two treatments.

In Study BLS-11-103 exposures of MMF following two 100 mg Bafiertam capsules were compared with one Tecfidera® 240 mg. The results showed that only AUC0-t and AUC0-inf values of MMF met the acceptance criteria for bioequivalence between BLS-11 200 mg and the reference product; Cmax was slightly higher after administration of BLS-11 200 mg and did not meet the acceptance criteria.

The applicant demonstrated bioequivalence (BE) of MMF exposure following administration of two 95 mg Bafiertam delayed release capsules and one Tecfidera® 240 mg DMF delayed release capsule in a pivotal bioequivalence Study BLS-11-104.Therefore, the dose strength of 95 mg MMF was selected for subsequent food and dose proportionality studies.

Figures below depict the plasma concentration time profile and statistical comparisons for MMF following administration of the commercial to be marketed formulation (TBM) under fed and fasting conditions.

Figure 1: Mean Plasma MMF Concentration-Time Profiles Following a Single Oral Dose of BLS-11 190 mg MMF (Treatment A) and a Single Oral Dose of Tecfidera® 240 mg DMF (Treatment B)

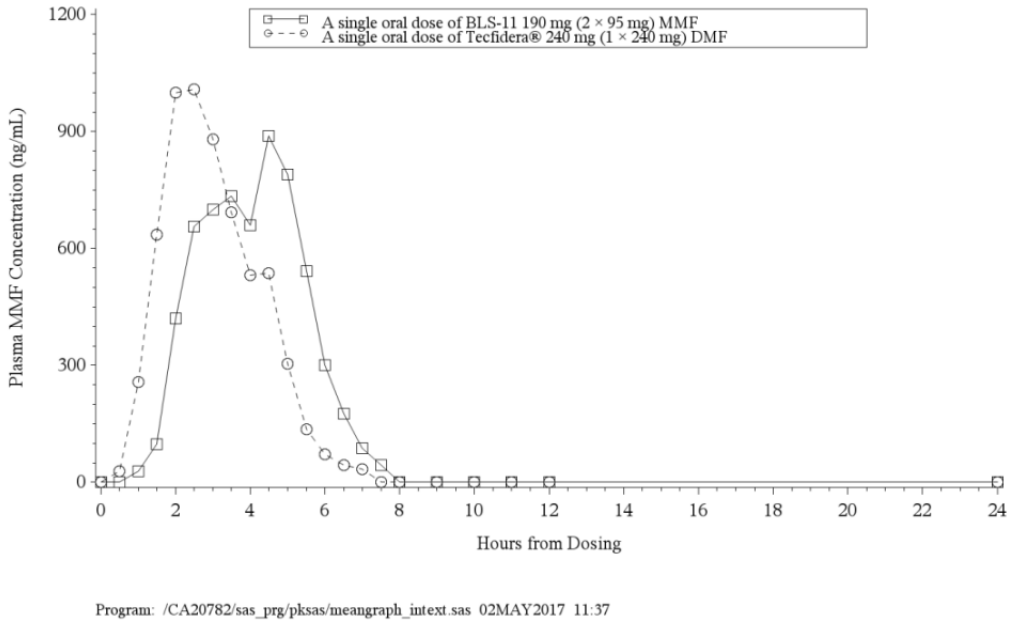


Figure 2: Statistical Comparisons of Pharmacokinetic Parameters of MMF Following a Single Oral Dose of BLS-11 190 mg (2 × 95 mg) MMF Versus a Single Oral Dose of Tecfidera® 240 mg (1 × 240 mg) DMF.

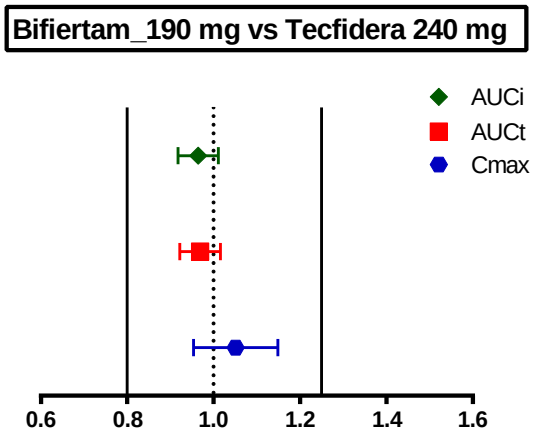


Table 1: Summary of statistical comparisons between BLS-11 190 mg (2 × 95 mg) MMF (Treatment A) Versus a Single Oral Dose of Tecfidera® 240 mg (1 × 240 mg) DMF (Treatment B)

	Treatment A (Test)		Treatment B (Reference)				
Parameter	Geometric LSMs	n	Geometric LSMs	n	GLSM Ratio (%)	90% Confidence Interval	Intra-subject CV%
AUC0-t (ng*hr/mL)	2955	49	3053	49	96.80	92.18 - 101.64	14.48
AUC0-inf (ng*hr/mL)	3002	48	3116	48	96.35	91.81 - 101.12	14.16
Cmax (ng/mL)	1760	49	1680	49	104.84	95.54 - 115.05	27.93

Treatment A: A single oral dose of BLS-11 190 mg (2 × 95 mg) MMF (Test)
Treatment B: A single oral dose of Tecfidera® 240 mg (1 × 240 mg) DMF (Reference)
Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs derived from the ANOVA.
Geometric Least-Squares Mean Ratio (GLSM) = 100%*(test/reference)
Intra-subject CV% was calculated as 100% x square root(exp[MSE]-1), where MSE = Residual variance from ANOVA.

Exposure response relationship for MMF is unknown, Tmax of MMF following administration of Bafiertam was approximately 1.5 hours delayed when compared LD. The delay in Tmax is not considered significant based on mechanism of action of monomethyl fumarate which is administered chronically. Even though there was a delay in Tmax in the presence of food LD was labelled to be taken with or without food.

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed dosing regimen is acceptable. The dosing regimen of Bafiertam and Tecfidera is based bioequivalence of MMF exposures. Following table represents the dosing regimen for Bafiertam in comparison with Tecfidera dosing regimen.

	BLS-11 95 mg	**BLS-11 190 mg**	**Tecfidera 120 mg**	**Tecfidera 240 mg**
Strength	95 mg	2 x 95 mg	120 mg	240 mg
Formulation	delayed-release capsule	delayed-release capsule	delayed-release capsule	delayed-release capsule
Dosing regimen	1 capsule	2 capsules	1 capsule	1 capsule
Frequency	b.i.d	b.i.d	b.i.d	b.i.d
Dosing Regimen	Starting dose: one 95 mg capsule bid for 7 days followed by 2x95 mg capsules bid, maintenance dose		Starting dose: one 120 mg capsule bid for 7 days followed by 2x120 mg capsules bid, maintenance dose	
Total Daily Dose	190 mg	380 mg	240 mg	480 mg

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

No. There is no need for an alternative dose or dosing regimen for subpopulation based on the intrinsic factors (see LD NDA 204063 clinical pharmacology review).

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

No. There is no significant food effect on MMF to impact its clinical responses.

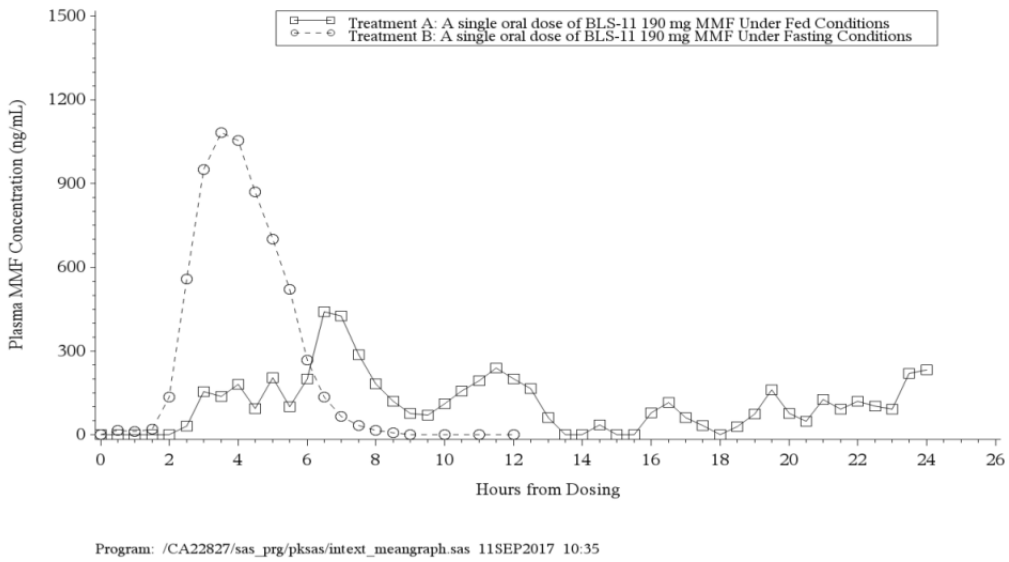
The applicant evaluated the effect of a high fat meal on exposure to MMF after administration of BAFIERTAM in Study BLS-11-105 and Study BLS-11-106.Two food effect studies were conducted to characterize the effect of a high-fat meal on the bioavailability of BLS-11, 2 x 95 capsules. Both studies were randomized crossover in design with at least 4 days between the two treatments (Fasted and Fed). Study BLS-11-105 was first carried out with infrequent blood sampling for both treatment arms (every 30 minutes for 8 hours post-dosing, and then hourly between 8 and 12 hours); a final sample was collected at 24 hours post dose with no samples collected between 12 and 24 hours post dose, due to the significantly delayed absorption.

Study BLS-11-106 is a well-designed food effect study. There is no significant food effect on AUC of MMF but high-fat food decreased Cmax of MMF by 20%. The median Tmax was delayed from 4 hours and 10.75 hours in the presence of high fat meal. Although the dose/exposure response relationship for MMF is unknown, this finding is similar to the RLD, TECFIDERA, (decreased Cmax by 40% and delayed Tmax from 2 hours to 5.5 hours). And monomethyl fumarate is indicated for chronic administration. Therefore, BAFIERTAM could be administered with or without food.

Please note that in the BAFIERTAM studies, unlike food may reduce the incidence of flushing for LD, the presence of food did not impact the incidence of flushing.

Figures below depict the plasma concentration time profile and statistical comparisons for MMF following administration of the commercial to be marketed formulation (TBM) under fed and fasting conditions.

Figure 3: Mean Plasma MMF Concentration-Time Curves Following a Single Dose of BLS-11 190 mg MMF Under Fed and Fasted Conditions (Study BLS-11-106)



Reviewer's Comment: Similar MMF PK profile characterized by several small peaks for MMF was observed following administration of TECFIDERA. The average PK profile is not representative of individual PK profiles since each subject had peak plasma concentrations at different time points (see figure below).

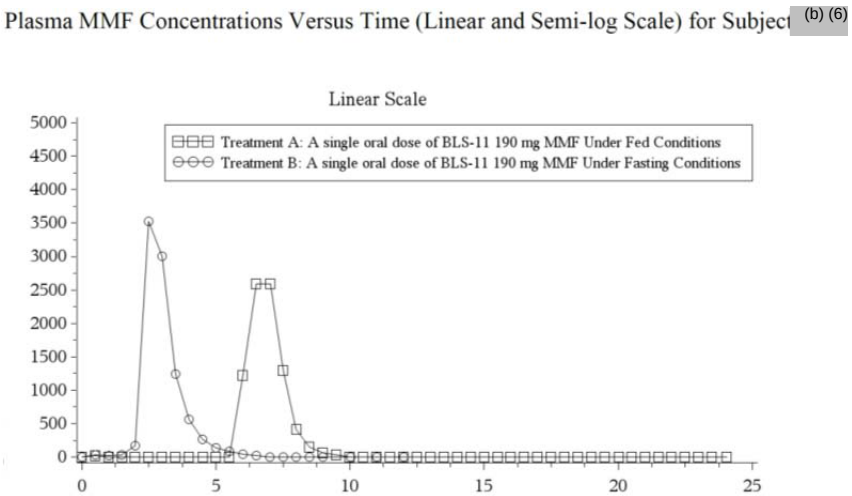


Figure 4: Statistical Comparisons of Pharmacokinetic Parameters of MMF Following a Single Oral Dose of BLS-11 190 mg MMF Under Fed Conditions Versus Fasting Conditions

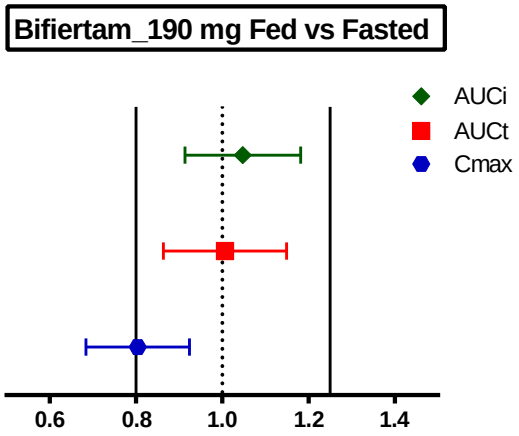


Table 2: Summary of Statistical Comparisons of Pharmacokinetic Parameters of MMF Following a Single Oral Dose of BLS-11 190 mg MMF Under Fed Conditions (Treatment A) Versus Fasting Conditions (Treatment B)

	Treatment A (Test)		Treatment B (Reference)				
PK Parameter	Geometric LSMs	n	Geometric LSMs	n	GLSM Ratio (%)	90% Confidence Interval	Intra-subject CV%
AUC0-t (ng*hr/mL)	3134	22	3135	23	99.97	86.71 - 115.27	27.84
AUC0-inf (ng*hr/mL)	3293	21	3160	23	104.20	91.66 - 118.45	24.31
Cmax (ng/mL)	1530	22	1920	23	79.83	68.75 - 92.70	29.07

No new drug interaction studies were conducted using BAFIERTAM.

3.3.5 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Dose proportionality of MMF was demonstrated following single-dose administration of 1 x 95 mg and 2 x 95 mg Monomethyl Fumarate 95 mg Delayed Release Capsules in healthy subjects. The PK parameters of MMF were found to be essentially dose proportional (Study BLS-11-108).

Table: Summary of Statistical Comparisons of Dose Normalized PK Parameters Monomethyl Fumarate:

TREAMENT B vs TREATMENT A						
Parameter (N/N)	Geometric Least-squares Means Arithmetic Means (CV %)				Ratio of Geometric Least-squares Means	90% Confidence Interval	Intra-Subject CV (%)
	TRT B		TRT A				
AUCt (ng.h/mL) (16 /16)	1542.0 1629.0	(33.25)	1429.5 1508.7	(34.70)	107.87	95.25 - 122.16	20.18
AUCinf (ng.h/mL) (16 /16)	1557.5 1643.9	(33.01)	1457.3 1535.7	(34.19)	106.88	94.48 - 120.91	20.00
Cmax (ng/mL) (16 /16)	909.1 999.3	(40.47)	958.2 1053.9	(45.39)	94.88	75.89 - 118.62	37.05

Note: The maximum concentrations (Cmax) were essentially dose proportional may be due to higher variability when compared to other PK parameters

4. APPENDICES

4.1: Summary of Bioanalytical Method Validation and Performance

4.1.1 How are the active moieties identified and measured in the clinical pharmacology and biopharmaceutics studies?

A validated liquid chromatographic-tandem mass spectrometric (LC/MS/MS) bioanalytical methods were used to quantify plasma concentrations of monomethyl fumarate in human plasma. Monomethyl Fumarate-d5 was used as the internal standard. The lower limit of quantitation was 25 ng/mL. Following table describes the summary of method validation and performance.

Table 3: Summary of Bioanalytical Method Validation and Performance

Analytical Method used during validation	Determination of Monomethyl Fumarate in Human NaF/K-Oxalate/1.0% Phosphoric Acid Plasma (25- 2500 ng/mL) by LC-MS/MS (API 4000). Monomethyl Fumarate in Human Plasma, (b) (4) _2016.2.00Draft abbreviated as MoFu HP 2016.200D
Short description of the method	Sample pre-treatment involved protein precipitation and filtration of Monomethyl Fumarate from 0.1 mL of human plasma. Monomethyl Fumarate-d_5 was used as the internal standard. The compounds were identified and quantified using reversed-phase liquid chromatography with tandem mass spectrometric detection.
Biological matrix	Human Sodium Fluoride/Potassium-Oxalate Plasma
Analyte	Monomethyl Fumarate
Internal standard (IS)	Monomethyl Fumarate-d_5
Calibration concentrations (Units)	25.04 to 2503.60 ng/mL
Lower limit of quantification (Units)	25.04 ng/mL Accuracy : 100.6% Precision: 7.0%
Average recovery of drug (%)	77.7%
Average recovery of IS (%)	72.3%

QC concentrations (Units)	LLQC: 25.02 ng/mL LQC: 75.05 ng/mL MQC: 1250.80 ng/mL HQC: 2001.28 ng/mL
QC Interday accuracy range (%)	96.2 to 106.7%
QC Interday precision range (%)	4.9 to 7.0%
QC Intraday accuracy range (%)	94.0 to 103.0%
QC Intraday precision range (%)	1.9 to 9.4%
Bench top (Short term) stability in biological matrix at room temperature. (Observed change %)	24 hours at RT Stability QC without dimethyl fumarate, % change: 0.2% (LQC) and 0.8% (HQC) Stability QC with dimethyl fumarate, % change: 2.3% (LQC) and -0.2% (HQC)
Bench top (Short term) stability in biological matrix at 4°C (Observed change %)	22 hours at 4°C Stability QC without dimethyl fumarate, % change: 1.0% (LQC) and 1.6% (HQC) Stability QC with dimethyl fumarate, % change: 4.8% (LQC) and 0.1% (HQC)
Auto sampler storage stability (Observed change %) (same as processed stability at 4°C)	142 hours at 4°C Stability QC, % change at 4°C : -0.3% (LQC) and 0.1% (HQC)
Processed stability (Observed Change %)	142 hours at 4°C and at room temperature Stability QC, % change at 4°C : -0.3% (LQC) and 0.1% (HQC) Stability QC, % change at RT : 2.6% (LQC) and 1.6 % (HQC)
Interim storage stability in matrix (Observed Change %)	6 days at -20°C and at -70°C Stability QC, % change at -20°C: -5.6% (LQC) and -2.3 % (HQC) Stability QC, % change at -70°C: -4.4% (LQC) and -1.5% (HQC)
Whole Blood Stability (Observed Change %)	2.0 hours at 4°C % Change in the absence of dimethyl fumarate: -3.0% (LQC), -5.7% (HQC) % Change in the presence of dimethyl fumarate: -9.4% (LQC), -2.8% (HQC)
Short Term Working Solution Stability (Observed Change %)	69 hours at room temperature for working solution. % Change: -1.4%
Freeze and thaw stability (Observed Change %)	-20°C/RT, 3 cycles and -70°C/RT, 3 cycles Stability QC without dimethyl fumarate, % change at -20°C: -5.6% (LQC) and -1.7% (HQC) Stability QC with dimethyl fumarate, % change at -20°C: -2.5% (LQC) and -0.9% (HQC) Stability QC without dimethyl fumarate, % change at -70°C: -4.3% (LQC) and -1.9% (HQC) Stability QC with dimethyl fumarate, % change at -70°C: 3.0% (LQC) and -0.3% (HQC)
Dilution integrity	Concentration diluted 10-fold Accuracy: 102.6%, Precision: 5.1%
Selectivity	No interfering peaks noted in blank plasma samples
Interference from common drugs	No impact on quantitation
Carry over test	No significant carry over.

4.2 Clinical Pharmacokinetics

4.2.1 Individual Study Reports

BLS-11-103: 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.

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 product, Tecfidera® 240 mg dimethyl fumarate (DMF) delayed-release capsule, in healthy male and non-pregnant female subjects under fasting conditions.
- To evaluate bioequivalence of the test and reference products 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 under these conditions.

Study Design	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.
Study Population	Healthy Subjects (males and female) Age: 18-55 years BMI: 18 to 29.9 kg/m^2. 56 subjects were enrolled and 50 completed the study
Treatments	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 predose sample) up to 24 hours postdose for the determination of plasma concentrations of MMF.
Sampling:	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 postdose, in each period.
Analysis	Plasma MMF concentrations were measured by a validated liquid chromatographic-tandem mass spectrometric (LC/MS/MS) bioanalytical methods were used to quantify plasma concentrations of monomethyl fumarate in human plasma. Monomethyl Fumarate-d5 was used as the internal standard. The lower limit of quantitation was 25 ng/mL. The assay was performed immediately before starting the analysis of the samples

<table>
<tr><td></td><td>from this analytical study.

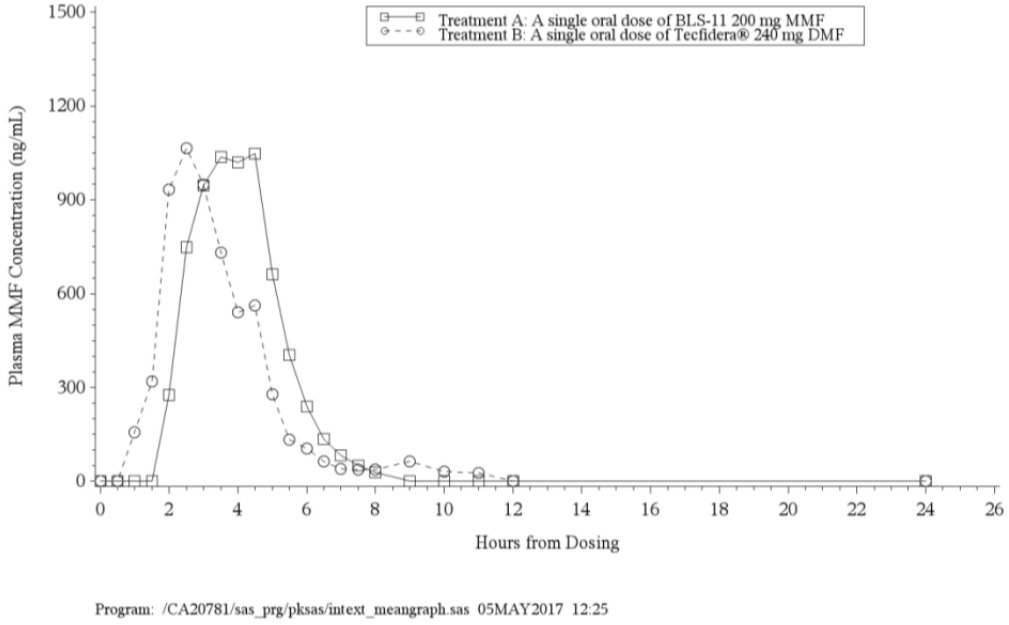
Summary of control results are presented in the table below.

<table>
<tr><th>Parameter</th><th>Quality Control Samples</th><th>Standard Curve Samples</th></tr>
<tr><td>Quality Control or Standard Curve Concentration (ng/mL)</td><td>75, 750, 1250 and 2000 ng/mL</td><td>25, 50, 100, 200, 400, 500, 1000, 1500, 2250 and 2500 ng/mL</td></tr>
<tr><td>Between Batch Precision (%CV)</td><td>1.5 to 7.9</td><td>1.8 to 5.0</td></tr>
<tr><td>Between Batch Accuracy (%RE)</td><td>-2.1 to 0.3</td><td>-3.9 to 2.8</td></tr>
<tr><td>Linearity</td><td colspan="2">Weighted linear equation ($1/X^2$), mean r= 0.9981</td></tr>
<tr><td>Linear Range (µg/mL)</td><td colspan="2">25 to 2500 ng/mL</td></tr>
<tr><td>Sensitivity (LLOQ, µg/mL)</td><td colspan="2">25 ng/mL</td></tr>
</table>
</td></tr>
<tr><td>Pharmacokinetic Assessments</td><td>The pharmacokinetic parameters were calculated, using calculated from the plasma MMF concentration-time data using noncompartmental methods with Phoenix® WinNonlin® Version 6.3 or higher. The following pharmacokinetic parameters were derived for each subject after each of the 2 treatments administered: Cmax, Tmax, tlag, Ke, AUC0-t, AUC0-inf and Frel. The plasma concentration-time data for MMF was analyzed using noncompartmental methods using Phoenix® WinNonlin® Version 6.3. The plasma PK parameters of interest following a single dose of BLS-11 190 mg (2 x 95 mg) MMF and Tecfidera® 240 mg DMF included: AUC0-t, AUC0-inf, AUC%extrap, Cmax, tmax, Kel, and t½.</td></tr>
<tr><td>Safety Assessments</td><td>Adverse events (AEs), standard laboratory assessments, vital signs, electrocardiograms and physical examination.</td></tr>
<tr><td>Statistical Methods</td><td>To assess the bioequivalence of the two formulations of stiripentol, an analysis of variance followed by the calculation of the 90 % confidence intervals for the ratio test/reference of Cmax and AUC were performed. Values of Cmax and AUC were a priori log-transformed. Bioequivalence was concluded if the corresponding 90 % confidence intervals for the ratio of the mean were included between 0.80 and 1.25 for AUC0-∞ (or AUCO-t) and Cmax. 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 AUC0-t, AUC0-inf, and Cmax 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.</td></tr>
</table>

RESULTS:

Following figure represents mean plasma MMF concentration-time profiles following a single oral dose of BLS-11 200 mg MMF (Treatment A) and a single oral dose of Tecfidera® 240 mg DMF (Treatment B) on linear and semi-log scale are presented in the following figures.

Mean Plasma MMF Concentration-Time Curves Following a Single Oral Dose of BLS-11 200 mg MMF (Treatment A) and a Single Oral Dose of Tecfidera® 240 mg DMF (Treatment B)



Following administration of a single oral dose of BLS-11 200 mg MMF (Treatment A), there was a delay in the rise of MMF concentration up-to 1.5 hours. Plasma MMF remained BLQ in the majority of subjects until at least 2 hours postdose, with Cmax of MMF achieved at 4 hours postdose.

Following a single oral dose of Tecfidera® 240 mg DMF (Treatment B), plasma MMF concentrations were measurable in the majority of the subjects at 1 hour postdose, with Cmax of MMF achieved at 2.6 hours postdose. The plasma concentrations of MMF for > 50% of subjects fell to BLQ again starting at 7 and 6.5 hours postdose for Treatments A and B, respectively.

Following tables represents statistical comparisons and mean pharmacokinetic parameters.

Summary of Statistical Comparisons of Pharmacokinetic Parameters of MMF Following a Single Oral Dose of BLS-11 200 mg MMF (Treatment A) Versus a Single Oral Dose of Tecfidera® 240 mg DMF (Treatment B)

	Treatment A (Test)		Treatment B (Reference)				
PK Parameter	Geometric LSMs	n	Geometric LSMs	n	GLSM Ratio (%)	90% Confidence Interval	Intra-subject CV%
AUC0-t (ng*hr/mL)	3264	49	3021	49	108.06	101.83 - 114.68	17.66
AUC0-inf (ng*hr/mL)	3387	43	3073	43	110.20	103.66 - 117.16	16.98
Cmax (ng/mL)	2150	49	1740	49	124.14	110.47 - 139.50	35.44

Treatment A: A single oral dose of BLS-11 200 mg MMF (Test)
Treatment B: A single oral dose of Tecfidera® 240 mg DMF (Reference)
Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs derived from the ANOVA.
Geometric least-square means (GLSM) Ratio = 100%*(test/reference)
Intra-subject CV% was calculated as 100% x square root(exp[MSE]-1), where MSE = Residual variance from ANOVA.

Summary of Pharmacokinetic Parameters of MMF Following a Single Oral Dose of BLS-11 200 mg MMF (Treatment A) and a Single Oral Dose of Tecfidera® 240 mg DMF (Treatment B)

	Treatment A		Treatment B	
Pharmacokinetic Parameters		n		n
AUC0-t (ng*hr/mL)	AM: 3369 (36.6%) GM: 3264 (33.4%) 0.00, (3278,7390)	50	AM: 3122 (24.5%) GM: 3027 (25.8%) 1759, (3253,5204)	50
AUC0-inf (ng*hr/mL)	AM: 3464 (33.0%) GM: 3292 (33.1%) 1634, (3367,7422)	49	AM: 3173 (24.2%) GM: 3081 (25.3%) 1780, (3318,5222)	44
AUC%extrap (%)	0.85 ± 0.32	49	0.91 ± 0.44	44
Cmax (ng/mL)	AM: 2320 (48.4%) GM: 2160 (46.5%) 0.00, (2240,6380)	50	AM: 1870 (36.9%) GM: 1750 (40.4%) 613, (1800,3650)	50
tmax (hr)	4.00 (2.00 , 6.50)	49	2.56 (1.00 , 9.01)	50
Kel (1/hr)	1.4362 ± 0.2363	49	1.3895 ± 0.2361	44
t½ (hr)	0.497 ± 0.0892	49	0.515 ± 0.105	44

Treatment A: A single oral dose of BLS-11 200 mg MMF
Treatment B: A single oral dose of Tecfidera® 240 mg DMF
AUC and Cmax values are presented as arithmetic mean (CV%), Geom Mean (Geom CV%), and median (min, max).
tmax is presented as median (min, max)
Other parameters are presented as arithmetic mean (± SD).
AM = Arithmetic mean, GM = Geometric mean

CONCLUSIONS:

Test formulation BLS-11 200 mg did not meet the bioequivalence criteria for Cmax. However, AUC0-t and AUC0-inf values of MMF met the acceptance criteria for bioequivalence between the test and listed drug.

BLS-11-104: 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

Objectives:

- 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 evaluate bioequivalence of the test and reference products after single-dose administration under fasting conditions.
- To evaluate the safety and tolerability.

Study Design	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
Study Population	Healthy Subjects (males and female) Age: 18-55 years BMI: 18 to 29.9 kg/m^2. 56 subjects were enrolled and 49 completed the study
Treatments	The test product was BLS-11 (MMF). Subjects were administered a single oral dose of 190 mg MMF (2 × 95 mg delayed-release capsule; Lot No.: 14700847MA) at Hour 0 on Day 1, with 240 mL of water. The reference product was Tecfidera®. Subjects were administered 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. In each period, subjects received a single oral dose of test and reference products, followed by blood sampling (including predose samples) up to 24

<table>
<tr><td></td><td>hours postdose for the determination of plasma concentrations of MMF. There was a washout period of at least 2 days between the 2 doses.</td></tr>
<tr><td>Sampling:</td><td>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 postdose, in each period.</td></tr>
<tr><td>Analysis</td><td>Plasma MMF concentrations were measured by a validated liquid chromatographic-tandem mass spectrometric (LC/MS/MS) bioanalytical methods were used to quantify plasma concentrations of monomethyl fumarate in human plasma. Monomethyl Fumarate-d5 was used as the internal standard. The lower limit of quantitation was 25 ng/mL. The assay was performed immediately before starting the analysis of the samples from this analytical study.

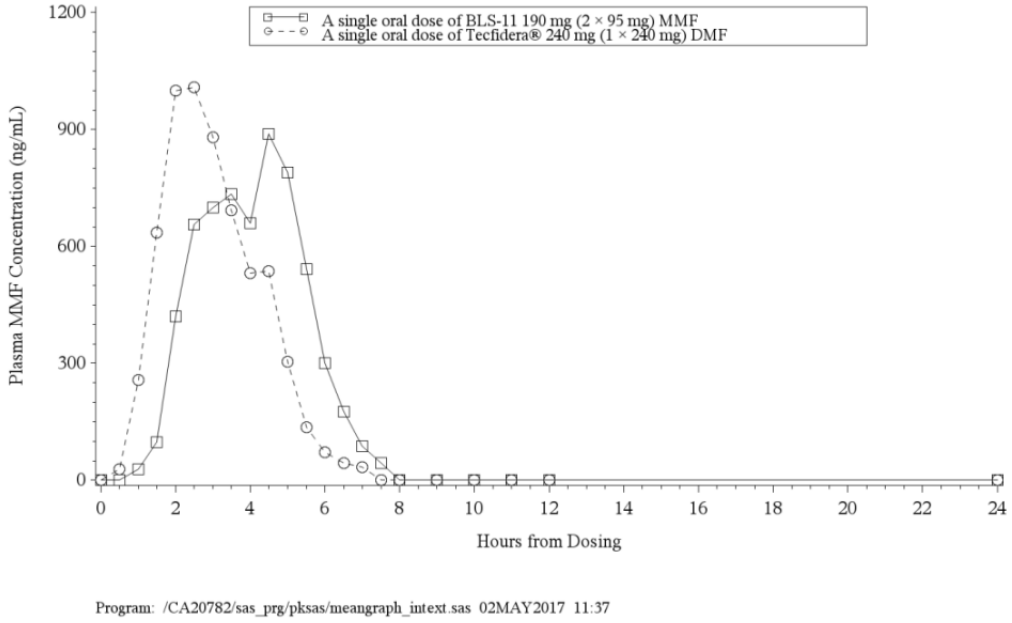
Summary of control results are presented in the table below.
<table>
<tr><th>Parameter</th><th>Quality Control Samples</th><th>Standard Curve Samples</th></tr>
<tr><td>Quality Control or Standard Curve Concentration (ng/mL)</td><td>75, 750, 1250 and 2000 ng/mL</td><td>25, 50, 100, 200, 400, 500, 1000, 1500, 2250 and 2500 ng/mL</td></tr>
<tr><td>Between Batch Precision (%CV)</td><td>2.4 to 3.9</td><td>1.4 to 6.5</td></tr>
<tr><td>Between Batch Accuracy (%RE)</td><td>-2.3 to 1.3</td><td>-4.2 to 3.1</td></tr>
<tr><td>Linearity</td><td colspan="2">Weighted linear equation ($1/X^2$), mean r= 0.9978</td></tr>
<tr><td>Linear Range (µg/mL)</td><td colspan="2">25 to 2500 ng/mL</td></tr>
<tr><td>Sensitivity (LLOQ, µg/mL)</td><td colspan="2">25 ng/mL</td></tr>
</table>
</td></tr>
<tr><td>Pharmacokinetic Assessments</td><td>The pharmacokinetic parameters were calculated, using noncompartmental methods with Phoenix® WinNonlin® Version 6.3 or higher.The following pharmacokinetic parameters were derived for each subject after each of the 2 treatments administered: AUC0-t, AUC0-inf, AUC%extrap, Cmax, tmax, Kel, and t½.</td></tr>
<tr><td>Safety Assessments</td><td>Adverse events (AEs), standard laboratory assessments, vital signs, electrocardiograms and physical examination.</td></tr>
<tr><td>Statistical Methods</td><td>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 AUC0-t, AUC0-inf, and Cmax 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</td></tr>
</table>

	treatments. Bioequivalence was concluded if the corresponding 90 % confidence intervals for the ratio of the mean were included between 0.80 and 1.25 for AUC0-∞ (or AUC0-t) and Cmax.

RESULTS:

Figure below represents mean plasma MMF concentration-time profiles following a single oral dose of BLS-11 190 mg (2 × 95 mg) MMF (Treatment A) and a single oral dose of Tecfidera® 240 mg (1 × 240 mg) DMF (Treatment B) on linear scale.

Mean Plasma MMF Concentration-Time Profiles Following a Single Oral Dose of BLS-11 190 mg MMF (Treatment A) and a Single Oral Dose of Tecfidera® 240 mg DMF (Treatment B).



There was a delay in the rise of MMF concentration following Treatment A, plasma MMF remained BLQ for > 50% of subjects until 2 hours postdose, with mean peak plasma concentration of MMF achieved about 4.5 hours after dosing.

For Treatment B, BLQ values were observed in > 50% of subjects only until 0.5 hour postdose and the peak plasma MMF concentration was attained at approximately 2.5 hours postdose. The plasma concentrations of MMF fell to BLQ for > 50% of subjects again after 7.5 and 7 hours postdose for Treatments A and B, respectively.

Following table represents summary of statistical comparisons between the two treatments.

Summary of Plasma Pharmacokinetics of Plasma MMF Following a Single Oral Summary of Statistical Comparisons of Pharmacokinetic Parameters of MMF Following a Single Oral Dose of BLS-11 190 mg (2 × 95 mg) MMF (Treatment A) Versus a Single Oral Dose of Tecfidera® 240 mg (1 × 240 mg) DMF (Treatment B)

	Treatment A (Test)		Treatment B (Reference)				
Parameter	Geometric LSMs	n	Geometric LSMs	n	GLSM Ratio (%)	90% Confidence Interval	Intra-subject CV%
AUC0-t (ng*hr/mL)	2955	49	3053	49	96.80	92.18 - 101.64	14.48
AUC0-inf (ng*hr/mL)	3002	48	3116	48	96.35	91.81 - 101.12	14.16
Cmax (ng/mL)	1760	49	1680	49	104.84	95.54 - 115.05	27.93

Treatment A: A single oral dose of BLS-11 190 mg (2 × 95 mg) MMF (Test)
Treatment B: A single oral dose of Tecfidera® 240 mg (1 × 240 mg) DMF (Reference)
Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs derived from the ANOVA.
Geometric Least-Squares Mean Ratio (GLSM) = 100%*(test/reference)
Intra-subject CV% was calculated as 100% x square root(exp[MSE]-1), where MSE = Residual variance from ANOVA.

The summary of plasma MMF PK parameters, based on a single oral dose of BLS-11 190 mg (2 × 95 mg) MMF or a single oral dose of Tecfidera® 240 mg (1 × 240 mg) DMF, is presented in in following table.

Summary of Plasma Pharmacokinetics of Plasma MMF Following a Single Oral Dose of BLS-11 190 mg (2 × 95 mg) MMF (Treatment A) and a Single Oral Dose of Tecfidera® 240 mg (1 × 240 mg) DMF (Treatment B)

	Treatment A		Treatment B	
Pharmacokinetic Parameters		n		n
AUC0-t (ng*hr/mL)	AM: 3051 (26.3%) GM: 2952 (26.4%) 1578, (3025,5894)	49	AM: 3145 (25.3%) GM: 3051 (25.0%) 1888, (3077,5679)	49
AUC0-inf (ng*hr/mL)	AM: 3081 (26.0%) GM: 2984 (25.9%) 1615, (3046,5916)	49	AM: 3203 (24.3%) GM: 3116 (23.9%) 1988, (3136,5707)	48
AUC%extrap (%)	1.29 ± 0.27	49	1.27 ± 0.35	48
Cmax (ng/mL)	AM: 1860 (32.5%) GM: 1760 (34.8%) 524, (1810,4060)	49	AM: 1770 (32.7%) GM: 1680 (33.8%) 763, (1650,3500)	49
tmax (hr)	4.03 (1.02, 6.01)	49	2.50 (1.01, 5.04)	49
Kel (1/hr)	1.2940 ± 0.2747	49	1.2722 ± 0.3488	48
t½ (hr)	0.566 ± 0.154	49	0.591 ± 0.185	48

Treatment A: A single oral dose of BLS-11 190 mg (2 × 95 mg) MMF
Treatment B: A single oral dose of Tecfidera® 240 mg (1 × 240 mg) DMF
AUC and Cmax values are presented as arithmetic mean (CV%), Geom Mean (Geom CV%), and median (min, max).
tmax values are presented as median (min, max).
Other parameters are presented as arithmetic mean (± SD)
AM = Arithmetic mean; GM = Geometric mean

CONCLUSIONS:

Administration of 190 mg (two 95 mg) Bafiertam (MMF) delayed release capsule was found to be bioequivalent to Tecfidera® 240 mg (DMF) delayed release capsule in terms of MMF exposure.

BLS-11-105: 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

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 under fed and fasting conditions.

Study Design	This study 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).
Study Population	Healthy Subjects (males and female) Age: 18-55 years BMI: 18 to 29.9 kg/m^2. 16 subjects were enrolled and 16 completed the study
Treatments	The test 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 fed conditions (high-fat meal). 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.

<table>
<tr><td>Sampling:</td><td>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 postdose, in each period.</td></tr>
<tr><td>Analysis</td><td>Plasma MMF concentrations were measured by a validated liquid chromatographic-tandem mass spectrometric (LC/MS/MS) bioanalytical methods were used to quantify plasma concentrations of monomethyl fumarate in human plasma. Monomethyl Fumarate-d5 was used as the internal standard. The lower limit of quantitation was 25 ng/mL. The assay was performed immediately before starting the analysis of the samples from this analytical study.

Summary of control results are presented in the table below.

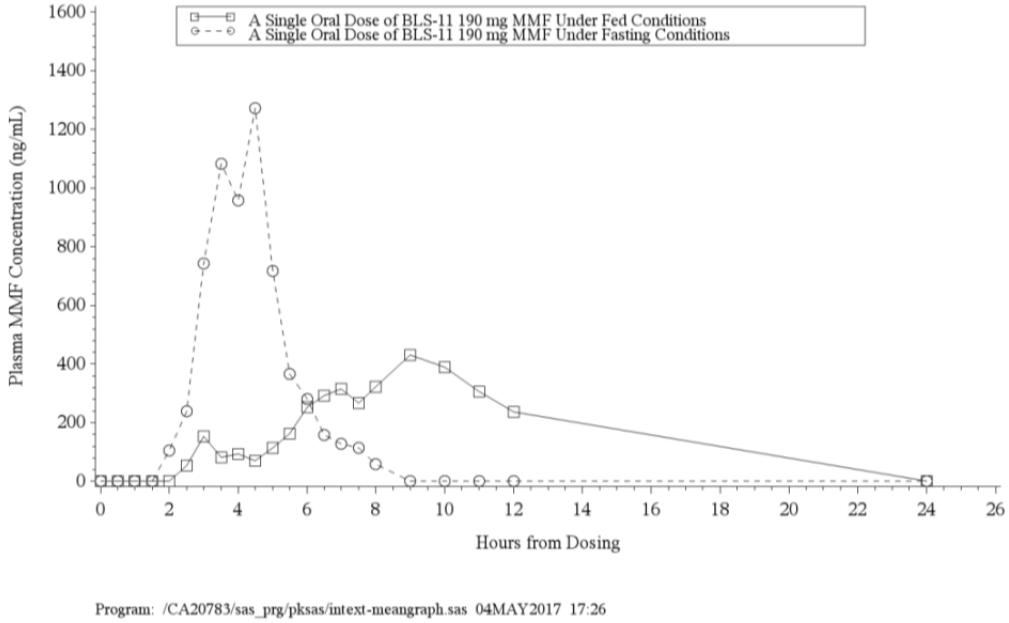
<table>
<tr><th>Parameter</th><th>Quality Control Samples</th><th>Standard Curve Samples</th></tr>
<tr><td>Quality Control or Standard Curve Concentration (ng/mL)</td><td>75, 750, 1250 and 2000 ng/mL</td><td>25, 50, 100, 200, 400, 500, 1000, 1500, 2250 and 2500 ng/mL</td></tr>
<tr><td>Between Batch Precision (%CV)</td><td>1.3 to 4.8</td><td>2.4 to 6.1</td></tr>
<tr><td>Between Batch Accuracy (%RE)</td><td>-5.3 to 1.8</td><td>-3.3 to 3.6</td></tr>
<tr><td>Linearity</td><td colspan="2">Weighted linear equation ($1/X^2$), mean r= 0.9968</td></tr>
<tr><td>Linear Range (µg/mL)</td><td colspan="2">25 to 2500 ng/mL</td></tr>
<tr><td>Sensitivity (LLOQ, µg/mL)</td><td colspan="2">25 ng/mL</td></tr>
</table>
</td></tr>
<tr><td>Pharmacokinetic Assessments</td><td>The pharmacokinetic parameters were calculated, using the WinNonlin. The following pharmacokinetic parameters were derived for each subject after each of the 2 treatments administered: Cmax, Tmax, tlag, Ke, AUC0-t, AUC0-inf and Frel. The plasma concentration-time data for MMF was analyzed using noncompartmental methods using Phoenix® WinNonlin® Version 6.3. The plasma PK parameters of interest following a single dose of BLS-11 190 mg (2 x 95 mg) MMF and Tecfidera® 240 mg DMF included: AUC0-t, AUC0-inf, AUC%extrap, Cmax, tmax, Kel, and t½.</td></tr>
<tr><td>Safety Assessments</td><td>Adverse events (AEs), standard laboratory assessments, vital signs, electrocardiograms and physical examination.</td></tr>
<tr><td>Statistical Methods</td><td>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 AUC0-t, AUC0-inf, and Cmax using SAS® PROC MIXED. The ANOVA model included sequence, treatment, and period as fixed effects, and subject nested within</td></tr>
</table>

	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.

RESULTS:

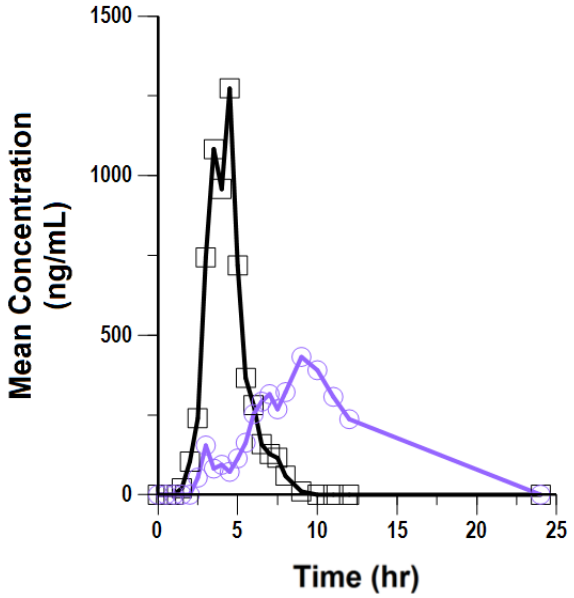
Following figure represents mean plasma MMF concentration-time profiles following a single oral dose of BLS-11 190 mg MMF under fed conditions (Treatment A) and fasting conditions (Treatment B) on linear scale.

Mean Plasma MMF Concentration-Time Curves Following a Single Oral Dose of BLS-11 190 mg MMF Under Fed Conditions (Treatment A) and Under Fasting Conditions (Treatment B)



Reviewer's Comment: The average PK profiles obtained from average plasma concentrations at each time point do not represent individual PK profiles specifically in fed state because variability in absorption at each timepoint. These were independently verified as shown in the figure below.

Reviewer Calculated: Mean Plasma MMF Concentration-Time Curves Following a Single Oral Dose of BLS-11 190 mg MMF Under Fed Conditions (Treatment A) and Under Fasting Conditions



Following administration of a single oral dose of BLS-11 190 mg MMF under fed conditions (Treatment A), there was a delay in the rise of MMF concentration where the peak plasma MMF concentration was attained after 9 hours postdose. Plasma MMF remained BLQ in > 50% of the subjects until 7 hours postdose.

Following administration of BLS-11 190 mg MMF under fasting conditions (Treatment B), the majority (> 50%) of the subjects had measurable plasma MMF concentrations by 3 hours postdose. The plasma concentrations of MMF in > 50% of subjects fell to BLQ again starting at 12 and 7.5 hours postdose for Treatments A and B, respectively. In 2 subjects, there were no quantifiable plasma MMF concentrations throughout the 12-hour period following Treatment A (fed conditions); there was no sampling between 12 and 24 hours postdose.

Reviewer's Comment: Similar MMF PK profile, characterized by several small peaks and delayed absorption was observed following treatment with listed drug, Tecfidera (NDA 204063).

Following tables represents statistical comparisons and mean pharmacokinetic parameters.

Summary of Statistical Comparisons of Pharmacokinetic Parameters of MMF Following a Single Oral Dose of BLS-11 190 mg MMF Under Fed Conditions (Treatment A) Versus Fasting Conditions (Treatment B)

	Treatment A (Test)		Treatment B (Reference)				
Parameter	Geometric LSMs	n	Geometric LSMs	n	GLSM Ratio (%)	90% Confidence Interval	Intra-subject CV%
AUC0-t (ng*hr/mL)	2220	14	2955	16	75.13	62.55 - 90.23	28.43
AUC0-inf (ng*hr/mL)	2732	6	2982	16	91.62	74.26 - 113.03	20.19
Cmax (ng/mL)	1270	14	1980	16	64.54	53.69 - 77.58	29.95

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
Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs derived from the ANOVA.
Geometric Mean Ratio (GMR) = 100*(test/reference)
Intra-subject CV% was calculated as 100 x square root(exp[MSE]-1), where MSE = Residual variance from ANOVA.

Summary of Plasma Pharmacokinetics of MMF Following a Single Oral Dose of BLS-11 190 mg MMF Under Fed Conditions (Treatment A) and Under Fasting Conditions (Treatment B)

Pharmacokinetic Parameters	Treatment A	Treatment B
AUC0-t (ng*hr/mL)	AM: 2047 (57.0%); GM: 2197 (37.3%) [n =16] [0.00,1924,4400]	AM: 3026 (22.1%); GM: 2955 (23.0%) [n =16] [1995,3008,4007]
AUC0-inf (ng*hr/mL)	AM: 2695 (36.8%); GM: 2569 (33.5%) [n =6] [1798,2395,4556]	AM: 3054 (22.1%); GM: 2982 (23.0%) [n =16] [2010,3030,4029]
AUC%extrap	2.31 ± 1.98 [n =6]	0.91 ± 0.32 [n =16]
Cmax (ng/mL)	AM: 1170 (54.1%); GM: 1270 (34.8%) [n =16] [0.00,1210,2470]	AM: 2030 (21.7%); GM: 1980 (24.7%) [n =16] [1100,2170,2560]
tmax (hr)	7.25 (3.00, 10.03) [n =14]	4.00 (3.00, 6.00) [n =16]
tlag (hr)	6.01 ± 1.87 [n =14]	2.57 ± 1.14 [n =16]
Kel (1/hr)	1.3591 ± 0.4434 [n =6]	1.5070 ± 0.2772 [n =16]
t½ (hr)	0.561 ± 0.193 [n =6]	0.477 ± 0.0987 [n =16]

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
AUC and Cmax values are presented as arithmetic-mean (CV%); Geom Mean (Geom CV %), and [min, med, max]
tmax values are presented as median (min, max).
Other parameters are presented as arithmetic mean (± SD).
AM = Arithmetic mean; GM = Geometric mean

Median tmax 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). Due to the delayed-release formulation, the minimum and maximum tmax values spanned over a great range, 3 to 10 hours for Treatment A and 3 to 6 hours for Treatment B; with median tlag for Treatment A of 6.25 hours and 2.50 hours postdose for Treatment B. The variation in tmax for Treatment A contributed to the multiphasic appearance of the above mean plasma MMF concentration versus time plots.

Note: There were no sampling time points for treatment A from 12 hours to 24 hours' time point. Plasma concentration was BLQ at 24 hour timepoint. Therefore, the sampling time points are not

adequate to calculate AUCs for treatment A. The sponsor conducted another food effect study (BLS-11-106) including frequent sampling upto 24 hours.

CONCLUSIONS:
A high-fat meal delayed the absorption and decreased the plasma exposure to MMF following administration of a single dose of BLS-11 190 mg. However, due to the lack of sampling between 12 and 24 hours postdose under fed conditions, the extent of the food effect cannot be accurately assessed.

BLS-11-106: 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

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 under fed and fasting conditions.

Study Design	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).
Study Population	Healthy Subjects (males and female) Age: 18-55 years BMI: 18 to 29.9 kg/m^2. 24 subjects were enrolled and 22 included in analysis
Treatments	The test 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 fed conditions (high-fat meal). 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.

<table>
<tr><td>Sampling:</td><td>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 postdose, in each period.</td></tr>
<tr><td>Analysis</td><td>Plasma MMF concentrations were measured by a validated liquid chromatographic-tandem mass spectrometric (LC/MS/MS) bioanalytical methods were used to quantify plasma concentrations of monomethyl fumarate in human plasma. Monomethyl Fumarate-d5 was used as the internal standard. The lower limit of quantitation was 25 ng/mL. The assay was performed immediately before starting the analysis of the samples from this analytical study.

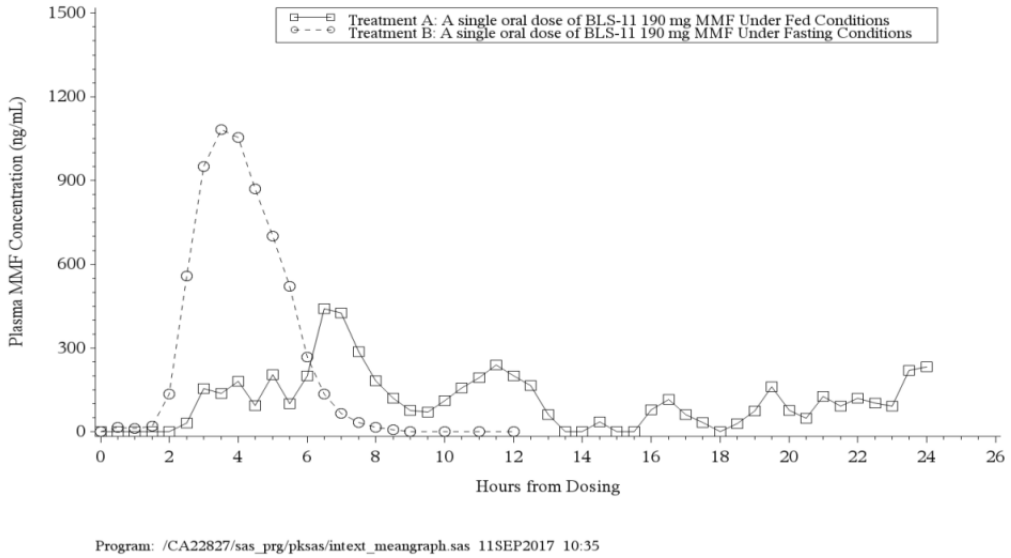
Summary of control results are presented in the table below.
<table>
<tr><th>Parameter</th><th>Quality Control Samples</th><th>Standard Curve Samples</th></tr>
<tr><td>Quality Control or Standard Curve Concentration (ng/mL)</td><td>75, 750, 1250 and 2000 ng/mL</td><td>25, 50, 100, 200, 400, 500, 1000, 1500, 2250 and 2500 ng/mL</td></tr>
<tr><td>Between Batch Precision (%CV)</td><td>4.2 to 7.5</td><td>2.5 to 5.6</td></tr>
<tr><td>Between Batch Accuracy (%RE)</td><td>-10.8 to 5.9</td><td>-6.2 to 3.9</td></tr>
<tr><td>Linearity</td><td colspan="2">Weighted linear equation ($1/X^2$), mean r= 0.9968</td></tr>
<tr><td>Linear Range (µg/mL)</td><td colspan="2">25 to 2500 ng/mL</td></tr>
<tr><td>Sensitivity (LLOQ, µg/mL)</td><td colspan="2">25 ng/mL</td></tr>
</table></td></tr>
<tr><td>Pharmacokinetic Assessments</td><td>The pharmacokinetic parameters were calculated, using the WinNonlin. The following pharmacokinetic parameters were derived for each subject after each of the 2 treatments administered: Cmax, Tmax, tlag, Ke, AUC0-t, AUC0-inf and Frel. The plasma concentration-time data for MMF was analyzed using noncompartmental methods using Phoenix® WinNonlin® Version 6.3. The plasma PK parameters of interest following a single dose of BLS-11 190 mg (2 x 95 mg) MMF and Tecfidera® 240 mg DMF included: AUC0-t, AUC0-inf, AUC%extrap, Cmax, tmax, Kel, and t½.</td></tr>
<tr><td>Safety Assessments</td><td>Adverse events (AEs), standard laboratory assessments, vital signs, electrocardiograms and physical examination.</td></tr>
<tr><td>Statistical Methods</td><td>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 AUC0-t, AUC0-inf, and Cmax using SAS® PROC MIXED. The ANOVA model included sequence, treatment, and period as fixed effects, and subject nested within</td></tr>
</table>

	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.

RESULTS:

Following figure represents mean plasma MMF concentration-time profiles following a single oral dose of BLS-11 190 mg MMF under fed conditions (Treatment A) and a single oral dose of BLS-11 190 mg MMF under fasting conditions (Treatment B) on linear and semi-log scale are presented in the figures below.

Mean Plasma MMF Concentration-Time Curves Following a Single Dose of BLS-11 190 mg MMF Under Fed and Fasted Conditions



Following administration of a single oral dose of BLS-11 190 mg MMF under fed conditions (Treatment A), there was a delay in the rise of MMF concentration, the peak plasma MMF concentration was attained at approximately 6.5 hours postdose. Under fasting conditions (Treatment B), Cmax was achieved at approximately 3.5 hours postdose. 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.

The above figures of the mean MFF concentration versus time profiles following Treatment A are not representative of the individual subject profiles since the peak plasma MMF concentrations occurred at different times over a wide range (from 3 to 24 hours postdose) in individual subjects following a single oral dose of 190 mg BLS-11 under fed conditions.

Reviewer's Comment: Similar average MMF PK profile, characterized by several small peaks and delayed absorption was observed following treatment with listed drug, Tecfidera (NDA 204063).

Following tables represents statistical comparisons and mean pharmacokinetic parameters.

Summary of Statistical Comparisons of Pharmacokinetic Parameters of MMF Following a Single Oral Dose of BLS-11 190 mg MMF Under Fed Conditions (Treatment A) Versus Fasting Conditions (Treatment B)

	Treatment A (Test)		Treatment B (Reference)				
PK Parameter	Geometric LSMs	n	Geometric LSMs	n	GLSM Ratio (%)	90% Confidence Interval	Intra-subject CV%
AUC0-t (ng*hr/mL)	3134	22	3135	23	99.97	86.71 - 115.27	27.84
AUC0-inf (ng*hr/mL)	3293	21	3160	23	104.20	91.66 - 118.45	24.31
Cmax (ng/mL)	1530	22	1920	23	79.83	68.75 - 92.70	29.07

Summary of Plasma Pharmacokinetics of MMF Following a Single Oral Dose of BLS-11 190 mg MMF Under Fed and Fasted Conditions

	Treatment A		Treatment B	
Pharmacokinetic Parameters		n		n
AUC0-t (ng*hr/mL)	AM: 3358 (45.0%) GM: 3125 (37.7%) [1697, 2859,7796]	22	AM: 3260 (26.8%) GM: 3135 (30.4%) [1602, 3221,4595]	23
AUC0-inf (ng*hr/mL)	AM: 3467 (43.5%) GM: 3241 (36.6%) [1718, 2983,7819]	21	AM: 3286 (26.6%) GM: 3162 (30.2%) [1631, 3250,4628]	23
AUC%extrap (%)	1.67 ± 2.81	21	0.86 ± 0.28	23
Cmax (ng/mL)	AM: 1690 (46.8%) GM: 1540 (45.1%) [742, 1360,3820]	22	AM: 2040 (35.8%) GM: 1910 (40.2%) [990, 2260,3530]	23
tmax (hr)	10.75 (3.00 , 24.00)	22	4.00 (2.50 , 5.51)	23
tlag (hr)	6.25 (0.00 , 22.50)	22	0.00 (0.00 , 3.53)	23
tlast (hr)	16.00 (7.00 , 24.22)	22	7.03 (5.50 , 8.51)	23
Kel (1/hr)	1.4086 ± 0.3105	21	1.2984 ± 0.2455	23
t½ (hr)	0.530 ± 0.199	21	0.554 ± 0.116	23

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
AUC and Cmax values are presented as arithmetic mean (CV%), Geom Mean (Geom CV%), and [min, med, max].
Tmax, tlag, and tlast values are presented as median (min, max)
Other parameters are presented as arithmetic mean (± SD).
AM = Arithmetic mean, GM = Geometric mean

The mean Cmax value 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 AUC0-t and AUC0-inf values were similar between both treatments. The mean AUC%extrap was < 2% for both Treatments A and B.

Median tmax 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). The large variation in tmax for Treatment A in individual subjects contributed to the appearance of multiple peaks in the mean plasma MMF concentration versus time profiles (figures above).

The mean t½ values for both treatments were comparable, at approximately 0.53 hours and 0.55 hours under fed (Treatment A) and fasting (Treatment B) conditions, respectively.

CONCLUSIONS:
Following administration of a single dose of BLS-11 190 mg with high-fat meal resulted in delayed the absorption of MMF and decreased the peak plasma concentration of MMF by approximately 20%

The extent of overall MMF exposure (AUC) of MMF was similar between fasted and fed states.

BLS-11-108: 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.

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.

Study Design	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 subjects
Study Population	Healthy Subjects (males and female) Age: 18-55 years BMI: 18 to 29.9 kg/m^2. 16 subjects were enrolled and 16 completed the study
Treatments	In each period, subjects received a single oral dose of BLS-11 95 mg delayed-release capsule (Treatment A) or a single oral dose of BLS-11 two 95 mg delayed-release capsules (Treatment B)

<table>
<tr><td>Sampling:</td><td>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 postdose, in each period.</td></tr>
<tr><td>Analysis</td><td>Plasma MMF concentrations were measured by a validated liquid chromatographic-tandem mass spectrometric (LC/MS/MS) bioanalytical methods were used to quantify plasma concentrations of monomethyl fumarate in human plasma. Monomethyl Fumarate-d5 was used as the internal standard. The lower limit of quantitation was 25 ng/mL. The assay was performed immediately before starting the analysis of the samples from this analytical study.

Summary of control results are presented in the table below.

<table>
<tr><th>Parameter</th><th>Quality Control Samples</th><th>Standard Curve Samples</th></tr>
<tr><td>Quality Control or Standard Curve Concentration (ng/mL)</td><td>75, 750, 1250 and 2000 ng/mL</td><td>25, 50, 100, 200, 400, 500, 1000, 1500, 2250 and 2500 ng/mL</td></tr>
<tr><td>Between Batch Precision (%CV)</td><td>4.2 to 7.5</td><td>2.5 to 5.6</td></tr>
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<tr><td>Pharmacokinetic Assessments</td><td>The pharmacokinetic parameters were calculated, using the WinNonlin. The following pharmacokinetic parameters were derived for each subject after each of the 2 treatments administered: Cmax, Tmax, tlag, Ke, AUC0-t, AUC0-inf and Frel. The plasma concentration-time data for MMF was analyzed using noncompartmental methods using Phoenix® WinNonlin® Version 6.3. The plasma PK parameters of interest following BLS-11 included: AUC0-t, AUC0-inf, AUC%extrap, Cmax, tmax, Kel, and t½.</td></tr>
<tr><td>Safety Assessments</td><td>Adverse events (AEs), standard laboratory assessments, vital signs, electrocardiograms and physical examination.</td></tr>
<tr><td>Statistical Methods</td><td>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 Cmax, AUCt, and AUCinf. 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 Cmax, AUCt, and AUCinf, were calculated after exponentiation of the</td></tr>
</table>

	difference in least squares means (Treatment B - Treatment A).

RESULTS:

Following table represents mean and dose normalized PK parameters following a single oral dose of BLS-11 95 mg MMF (Treatment A) and a single oral dose of two 95 mg BLS-11 95 mg MMF (Treatment B).

The descriptive statistics of PK parameter estimates of MMF for each treatment are presented in the following table:

Treatment	Statistics	AUC_{0-t} (ng.h/mL)	AUC_{0-inf} (ng.h/mL)	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)
A (1 x 95 mg capsule)	N	16	16	16	16	16
	Max	2583.7	2618.8	1960.0	6.00	0.89
	Min	705.7	727.2	497.0	2.00	0.35
	Median	1304.6	1328.4	866.5	4.00	0.47
	Mean	1508.7	1535.7	1053.9	3.85	0.52
	CV %	34.7	34.19	45.39	29.37	28.56
B (2 x 95 mg capsules)	N	16	16	16	16	16
	Max	5411.0	5433.7	3230.0	6.00	1.16
	Min	1502.5	1536.6	724.0	2.00	0.40
	Median	3265.7	3287.8	2120.0	3.51	0.53
	Mean	3258.0	3287.9	1998.7	3.58	0.57
	CV %	33.25	33.01	40.47	29.53	31.26

Results for Dose Normalized PK Parameters Monomethyl Fumarate:

TREAMENT B vs TREATMENT A

Parameter (N/N)	Geometric Least-squares Means Arithmetic Means (CV %)				Ratio of Geometric Least-squares Means	90% Confidence Interval	Intra-Subject CV (%)
	TRT B		TRT A				
AUCt (ng.h/mL) (16 /16)	1542.0 1629.0	(33.25)	1429.5 1508.7	(34.70)	107.87	95.25 - 122.16	20.18
AUCinf (ng.h/mL) (16 /16)	1557.5 1643.9	(33.01)	1457.3 1535.7	(34.19)	106.88	94.48 - 120.91	20.00
Cmax (ng/mL) (16 /16)	909.1 999.3	(40.47)	958.2 1053.9	(45.39)	94.88	75.89 - 118.62	37.05

The 90% confidence interval (CI) for AUCt and AUCinf parameter geometric least-squares means (GLSM) ratios were contained within 80% - 125%.

The 90% confidence interval for dose normalized Cmax GLSM ratio, 2 capsules vs. 1 capsule, was slightly outside the 80 to 125% confidence interval.

Note: The maximum concentrations (Cmax) was essentially dose proportional may be due to higher variability when compared to other PK parameters.

CONCLUSIONS:

- Following a single oral dose of BLS-11 95 mg MMF and a single oral dose of two 95 mg BLS-11 95 mg MMF the overall exposure (AUC) was dose proportional.
- The maximum exposure (Cmax) was essentially dose proportional.

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/s/

JAGAN MOHAN R PAREPALLY
10/24/2018

YUXIN MEN
10/24/2018