**Celerion Project No.: CA20782**

**Sponsor Project No.: 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

## GCP Statement

This study is to be performed in full compliance with the protocol, Good Clinical Practices (GCP), and applicable regulatory requirements. All required study documentation will be archived as required by regulatory authorities.

## Confidentiality Statement

# 1 PROTOCOL REVISION HISTORY

| Date/Name | Description |
|---|---|
| 12Dec2016<br>by David Goblot | Final Protocol |

## 2 PRINCIPAL INVESTIGATOR AND SPONSOR – SIGNATORIES

**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**

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## 2 PRINCIPAL INVESTIGATOR AND SPONSOR- SIGNATORIES

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# 5 SYNOPSIS

| | |
|---|---|
| Compound: | Monomethyl fumarate (MMF) |
| Study Phase and Type: | Phase 1 – Comparative Bioavailability |
| Study Objectives: | **Primary**:<br>To determine the pharmacokinetic (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 dimethyl fumarate (DMF) delayed-release capsule, in healthy male and non-pregnant female subjects under fasting conditions.<br>To assess if the test and reference products (indicated above) are bioequivalent in terms of the $C_{max}$ and AUC values of MMF after single-dose administration under fasting conditions.<br>**Secondary**:<br>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. |
| Summary of Study Design: | This is a single-dose, randomized, open-label, 2-way crossover study evaluating the comparative PK of the test product vs. the reference product under fasting conditions.<br>In each period, subjects will receive 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 predose sample) up to 24 hours postdose for the determination of plasma concentrations of MMF.<br>There will be a washout period of at least 2 days between the 2 doses.<br>The clinic will attempt to contact all subjects (including subjects who terminate the study early) using their standard procedures approximately 7 days after the last study drug administration to determine if any adverse events (AEs) have occurred since the last study visit. |

| | |
|---|---|
| Number of Subjects: | Fifty (50), healthy, adult male and non-pregnant female subjects will be enrolled.<br><br>Space constraints at the clinical research unit (CRU) may require subjects to be divided into 2 dosing groups of approximately equal size for dosing, as needed. Within each dosing group, subjects will be randomized to receive the test and reference products in a crossover fashion based on the randomization schedule. |
| Dosage, Dosage Form, Route, and Dose Regimen: | Treatments are described as follows:<br><br>Treatment A: (Test) a single oral dose administration of Banner Life Sciences 190 mg MMF (2 x 95 mg delayed-release capsules) on Day 1.<br><br>Treatment B: (Reference) a single oral dose administration of Biogen, Inc. Tecfidera® 240 mg DMF (1 x 240 mg delayed-release capsule) on Day 1.<br><br>All study drugs will be administered with approximately 240 mL of water following an overnight (at least 10 hours) fast. |
| Key Assessments: | **Pharmacokinetics:**<br>The following PK parameters will be calculated for MMF by noncompartmental methods, as appropriate or data permitting: AUC0-t, AUC0-inf, AUC%extrap, Cmax, tmax, Kel, and t½.<br>An analysis of variance (ANOVA) will be performed on the natural log (ln)-transformed AUC0-t, AUC0-inf, and Cmax, using the appropriate statistical procedure.<br>Bioequivalence criteria will be met if the 90% confidence intervals (CIs) for the ratios of geometric least-squares means (GLSM) of AUC0-inf, and Cmax of MMF of the Test (Treatment A) to the Reference (Treatment B) fall within the limit of 80.00 and 125.00%.<br>The tmax parameter will also be analyzed using an additional non-parametric test (Wilcoxon test) for information purpose and will not be used to determin product comparability.<br><br>**Safety:**<br>Safety will be monitored through vital sign measurements, clinical laboratory tests, and AEs. AEs will be tabulated and summary statistics for vital signs and clinical laboratory safety tests may be computed and provided, as deemed clinically appropriate. |

# 6 STUDY EVENTS FLOW CHART

| Events and Assessments [a] | Screening [b] | Dose Period 1 | | | Washout [c] | Dose Period 2 | | | FU [d] |
|---|---|---|---|---|---|---|---|---|---|
| | | Day -1 C-I | Day 1 | Day 2 | | Day -1 | Day 1 | Day 2 | |
| Informed Consent | X | | | | | | | | |
| Demographic Information | X | | | | | | | | |
| Complete Medical/Medication History | X | | | | | | | | |
| Update to Medical/Medication History | | X | | | | | | | |
| Full Physical Examination | X | | | | | | | | |
| Brief Physical Examination [e] | | X | | | | X | | X [n] | |
| Height, BMI | X | | | | | | | | |
| Weight | X | X | | | | | | | |
| Vital Signs (Sitting HR, BP and T) | X | | X [g] | X [h] | | | X [g] | X [h, n] | |
| Concomitant Medication Monitoring | | X | X | X | X | X | X | X [n] | |
| Clinical Laboratory Evaluations, Fasted [i] (Hematology, Serum Chemistry, and Urinalysis) | X | X | | | | | | X [n] | |
| Serum Pregnancy Test (♀only) | X | X | | | | | | X [n] | |
| Serum FSH (Postmenopausal ♀only) | X | | | | | | | | |
| Urine Drug / Alcohol / Cotinine Screen | X | X | | | | | | | |
| Serology (HIV, Hepatitis B, Hepatitis C) | X | | | | | | | | |
| 12-Lead Electrocardiogram | X | | X [f] | | | | | | |
| Study Drug Dosing [j] | | | X | | | | X | | |
| Begin Confinement | | X [k] | | | | | | | |
| End Confinement | | | | | | | | X [l] | |
| Blood for Pharmacokinetics | | | X [m] | X [m] | | | X [m] | X [m] | |
| Drug Dispensing and Accountability | | | X | | | | X | | |
| AE Monitoring | | | X | X | X | X | X | X [n] | X |

a: For details on Events and Assessments, refer to Section 11.

b: Within 21 days prior to the first study drug administration.

c: There will be a washout period of at least 2 days between the 2 doses.

d: The clinic will attempt to contact all subjects (including subjects who terminate the study early) using their standard procedures approximately 7 days after the last study drug administration to determine if any AEs has occurred since the last study visit.

e: Symptom-driven physical examination may be performed at other times, at the PI or designee's discretion.

f: Taken approximately2 hours prior to dosing.

g: Taken approximately 2 hours predose and at 2 hours postdose of each study drug.

h: Taken after the 24-hour postdose PK blood sample is obtained.

i: Subjects are reminded to fast for at least 8 hours prior to the blood draw for fasting clinical laboratory evaluation.

j: Study drug will be administered after an overnight fast (for at least 10 hours), followed by another 4 hours of fasting postdose.

k: Subjects will be admitted to the CRU on Day -1 of Dose Period 1, at the time indicated by the CRU.

l: Subjects will be discharged from the CRU after the last PK sample and the vital signs measurements are obtained at 24 hours postdose in Dose Period 2.

m: Venous blood samples (10 mL each) will be collected at 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.

n: To be performed at the scheduled time or prior to early termination from the study.

Abbreviations: ♀ = Females, AE = Adverse event, BP = Blood pressure, C-I = Check-in, CRU = Clinical research unit, FSH = Follicle-stimulating hormone, FU = Follow-up, HIV = Human immunodeficiency virus, HR = Heart rate, PI = Principal Investigator, PK = Pharmacokinetic, T = Temperature.

# 7 ABBREVIATIONS

| | |
|---|---|
| AE | Adverse event |
| ANOVA | Analysis of variance |
| AUC | Area under the concentration-time curve |
| AUC0-t | Area under the concentration-time curve, from time 0 (dosing time) to the last time point (tlast) with measurable drug concentration |
| AUC0-inf | Area under the concentration-time curve, from time 0 (dosing time) extrapolated to infinity |
| AUC%extrap | Percent of AUC0-inf extrapolated from last time point with measurable dug concentration to infinity |
| BE | Bioequivalence |
| BID | Twice a day |
| BMI | Body mass index |
| bpm | Beats per minute |
| °C | Degrees Celsius |
| CFR | Code of Federal Regulations |
| CI | Confidence interval |
| cm | Centimeter |
| Cmax | Maximum observed drug concentration |
| CRF | Case report form |
| CRU | Clinical research unit |
| CV | Coefficient of variation |
| CYP | Cytochrome P450 |
| DMF | Dimethyl fumarate |
| ECG | Electrocardiogram |
| FDA | Food and Drug Administration |
| FSH | Follicle-stimulating hormone |
| g | Gram |
| GCP | Good Clinical Practice |
| GLSM | Geometric least-squares means |
| HBsAg | Hepatitis B surface antigen |
| HCV | Hepatitis C virus |

| | |
|---|---|
| HIV | Human immunodeficiency virus |
| IB | Investigator's Brochure |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonisation |
| IND | Investigational New Drug |
| IRB | Institutional Review Board |
| Kel | Apparent terminal first-order decay rate constant |
| kg | Kilogram |
| L | Liter |
| ln | Natural logarithm |
| LSM | Least-squares means |
| $m^2$ | Meters squared |
| MedDRA® | Medical Dictionary for Regulatory Activities® |
| mg | Milligram |
| mL | Milliliter |
| MMF | Monomethyl fumarate |
| mmHg | Millimeter of mercury |
| MS | Multiple sclerosis |
| msec | Millisecond |
| No. | Number |
| P-gp | P-glycoprotein |
| PI | Principal Investigator |
| PK | Pharmacokinetic(s) |
| QA | Quality Assurance |
| RLD | Reference Listed Drug |
| rpm | Rotations per minute |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| TEAE | Treatment-emergent adverse event |
| tmax | Time to reach maximum observed drug concentration |
| t½ | Apparent plasma half-life |
| US | United States |

| | |
|---|---|
| USA | United States of America |
| UV | Ultraviolet |
| vs. | Versus |
| WHO | World Health Organization |

# 8 BACKGROUND AND RATIONALE

## 8.1 Background

### 8.1.1 Tecfidera® (Dimethyl Fumarate)

Tecfidera® is indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS). The mechanism by which DMF exerts its therapeutic effect in MS is unknown. After oral administration of Tecfidera®, DMF undergoes rapid presystemic hydrolysis by esterases, ubiquitous to the gastrointestinal tract, blood, and tissues, and is converted to its active metabolite, MMF, before it reaches the systemic circulation. Dimethyl fumarate is not quantifiable in plasma following oral administration of Tecfidera®.

Further metabolism of MMF occurs through the tricarboxylic acid cycle, with no involvement of the cytochrome P450 (CYP) system. Monomethyl fumarate, fumaric and citric acids, and glucose are the major metabolites in plasma.

Exhalation of $CO_2$ is the primary route of elimination, accounting for approximately 60% of the Tecfidera® dose. Renal and fecal elimination are minor routes of elimination, accounting for 16% and 1% of the dose respectively. Trace amounts of unchanged MMF were present in urine.

The terminal half-life (t½) of MMF is approximately 1 hour and no circulating MMF is present at 24 hours in the majority of individuals. Accumulation of MMF does not occur with multiple doses of Tecfidera®.

No potential drug interactions with DMF or MMF were identified in *in vitro* CYP inhibition and induction studies, or in P-glycoprotein studies. Single doses of interferon beta-1a or glatiramer acetate did not alter the PK of MMF. Aspirin, when administered approximately 30 minutes before Tecfidera®, did not alter the PK of MMF.

DMF and the metabolite, MMF, have 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.

The most common adverse reactions (incidence ≥10% and ≥2% more than placebo) for Tecfidera® were flushing, abdominal pain, diarrhea, and nausea. The incidence of flushing may be reduced by administration of Tecfidera® with food. Alternatively, administration of non-enteric coated aspirin (up to a dose of 325 mg) 30 minutes prior to Tecfidera® dosing may reduce the incidence or severity of flushing.

Refer to the approved US product label for detailed background information on Tecfidera®.[1]

### 8.1.2 BLS-11 (Monomethyl Fumarate)

As described in Section 8.1.1 above, DMF is rapidly and completely metabolized to MMF, an active metabolite.

Two pilot PK studies, Study 1980 and Study 1981, were conducted in which MMF was administered directly to human subjects.

These studies evaluated the PK and safety and tolerability of investigational formulations of MMF delayed-release capsules. These studies were conducted to select a formulation and dosage strength which is bioequivalent to Tecfidera® 240 mg and to evaluate the tolerability of MMF when administered directly to healthy subjects. of the investigational formulations were and In each study, Additionally, 2 different In both studies the relative bioavailability of the MMF formulations were compared to the Tecfidera® 240 mg delayed-release oral capsule.

The PK data obtained in the pilot studies informed the development of the formulation and dosage strength being investigated in this study. There were no new safety or tolerability findings.

Refer to the Investigator's Brochure (IB) for detailed background information on BLS-11 (MMF).[2]

## 8.2 Rationale

### 8.2.1 Rationale for this Study and Study Design

This study is designed to meet the objectives outlined in Section 9.

Banner Life Sciences plans to submit a new drug application for BLS-11, which contains MMF a new chemical entity that is the active metabolite of an approved drug.

The effectiveness of MMF administered as BLS-11 using a bioequivalence (BE) approach to the reference product, Tecfidera® (240 mg DMF delayed-release capsules) will be inferred.

This study will be 1 of 2 BE studies assessing 2 different test formulations of MMF in comparison to the reference formulation under fasting conditions. One (1) of the 2 test formulations will then be selected to assess BE under fed/fasting conditions.

Subjects will be randomized to treatment sequences to minimize assignment bias. A crossover design is used to control the variability between subjects. The washout period between doses is considered sufficient to prevent carryover effects of the treatments.

### 8.2.2 Rationale for the Dose Selection

The MMF dose, administered as BLS-11, to be examined in this study was selected based on the comparative (to Tecfidera®) BE data obtained in the [redacted]

### 8.2.3 Rationale for Endpoints

The primary objective of this study is to assess the BE of the test product versus the reference product based on the Cmax and AUC values of MMF determined after a single dose administered under fasting conditions. The active metabolite MMF will be used in the comparison since the parent drug, DMF, is rapidly and almost completely metabolized to MMF before reaching the systemic circulation and is generally not quantifiable in plasma. Statistical analysis will be performed on ln-transformed Cmax and AUC values of MMF using ANOVA to determine if BE criteria is met based on the FDA Guidances.[3, 4]

## 9 STUDY OBJECTIVES AND ENDPOINTS

### 9.1 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) are bioequivalent in terms of the Cmax 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.

### 9.2 Study Endpoints

**Pharmacokinetics:**

The primary endpoints for BE assessment will be comparison of AUC0-inf and Cmax of MMF between treatments. In addition, AUC0-t will be compared between treatments.

Additional PK parameters AUC% extrap, tmax, Kel, and t½ of MMF will be computed for information.

**Safety:**

Safety endpoints will include vital signs, clinical laboratory tests, and AEs.

# 10 INVESTIGATIONAL PLAN

## 10.1 Overall Study Design and Plan

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

Fifty (50), healthy, adult male and non-pregnant female subjects will be enrolled. Space constraints at the CRU may require subjects to be divided into 2 dosing groups of approximately equal size for dosing, as needed.

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

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

In each period, subjects will receive 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 predose sample) up to 24 hours postdose for the determination of plasma concentrations of MMF.

There will be a washout period of at least 2 days between the 2 doses.

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

Discontinued subjects will not be replaced.

### 10.1.1 Confinement, Return Visits, and Follow-Up

Subjects will be 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 be required to remain at the CRU for longer at the discretion of the Principal Investigator (PI) or designee.

The clinic will attempt to contact all subjects (including subjects who terminate the study early) using their standard procedures approximately 7 days after the last study drug administration to determine if any AEs has occurred since the last study visit.

## 10.2 Risks and/or Benefits to Subjects

The dose of Tecfidera® (DMF) or BLS-11 (MMF) administered in this study is not anticipated to induce any potential risk or benefit to subjects participating in this study; the single dose of Tecfidera® is administered per the dosing recommendations found in the full prescribing information for Tecfidera® (DMF)[1] and the single dose of BLS-11 is not greater than the dose resulting from the administration of Tecfidera®.

The safety monitoring practices employed by this protocol (i.e., vital signs, clinical laboratory tests, and AE questioning) are adequate to protect the subjects' safety and should detect all expected treatment-emergent AEs (TEAEs).

There will be no direct health benefit for study participants from receipt of study drug. An indirect health benefit to the healthy subjects enrolled in this study is the free medical tests received at screening and during the study.

### 10.3 Selection of Study Population

#### 10.3.1 Inclusion Criteria

Subjects must fulfill ***all*** of the inclusion criteria and ***none*** of the exclusion criteria to be eligible for participation in the study, unless otherwise specified:

1. Healthy, adult, male or female, 18 - 55 years of age, inclusive, at screening.

2. Continuous non-smoker who has not used nicotine-containing products for at least 3 months prior to the first dose and throughout the study.

3. Body mass index (BMI) $\geq$ 18.5 and $\leq$ 29.9 kg/m$^2$ at screening.

4. Medically healthy as determined by the investigator or designee with no clinically significant medical history, physical examination, laboratory profiles, vital signs or ECGs, as deemed by the investigator or designee.

5. For a female of childbearing potential: not pregnant and either be sexually inactive (abstinent) for 14 days prior to the first dose and throughout the study or be using one of the following acceptable birth control methods:

   - hormonal oral contraceptives, vaginal ring, transdermal patch, or non-hormone or hormone releasing intrauterine device for at least 3 months prior to the first dose with either a physical (e.g. condom, diaphragm, or other) or a chemical (e.g., spermicide) barrier method from the time of screening and throughout the study.
   - Depot/implantable hormone (e.g., Depo-Provera®, Implanon®) for at least 3 months prior to the first dose and throughout the study.

   In addition, female subjects of childbearing potential will be advised to remain sexually inactive or to keep the same birth control method for at least 7 days following the last dose.

6. For a female of non-childbearing potential: must have undergone one of the following sterilization procedures at least 6 months prior to the first dose:

   - hysteroscopic sterilization;
   - bilateral tubal ligation or bilateral salpingectomy;

- hysterectomy;
- bilateral oophorectomy.

or be postmenopausal with amenorrhea for at least 1 year prior to the first dose and follicle-stimulating hormone (FSH) serum levels consistent with postmenopausal status as per investigator's or designee's judgment.

7. A non-vasectomized, male subject must agree to use a condom with spermicide or abstain from sexual intercourse during the study until 90 days beyond the last dose of study drug. (No restrictions are required for a vasectomized male provided his vasectomy has been performed 4 months or more prior to the first dose of study drug. A male who has been vasectomized less than 4 months prior to the first dose of study drug must follow the same restrictions as a non-vasectomized male).

8. For a male, must agree not to donate sperm from the first dose until 90 days after dosing.

9. Understands the study procedures in the informed consent form (ICF), and be willing and able to comply with the protocol.

### 10.3.2 Exclusion Criteria

Subjects must not be enrolled in the study if they meet any of the following criteria:

1. Subject is mentally or legally incapacitated or has significant emotional problems at the time of the screening visit or expected during the conduct of the study.

2. History or presence of clinically significant medical or psychiatric condition or disease in the opinion of the investigator or designee.

3. History of any illness that, in the opinion of the investigator or designee, might confound the results of the study or poses an additional risk to the subject by their participation in the study.

4. History or presence of alcoholism or drug abuse within the past 2 years prior to the first dose.

5. History or presence of hypersensitivity or idiosyncratic reaction to the study drugs or related compounds.

6. Female subjects with a positive serum pregnancy test at screening or check-in, or who are lactating.

7. Positive urine drug, alcohol, or cotinine results at screening or check-in.

8. Positive results at screening for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg) or hepatitis C virus (HCV).

9. Seated blood pressure is less than 90/40 mmHg or greater than 140/90 mmHg at screening.

10. Seated heart rate is lower than 40 bpm or higher than 99 bpm at screening.

11. Abnormal 12-lead ECG deemed clinically significant by the investigator or designee at screening or prior to the first dose.

12. Unable to refrain from or anticipates the use of any drug, including prescription and non-prescription medications, or herbal remedies, beginning 14 days prior to the first dose and throughout the study. Medication listed as part of acceptable birth control methods will be allowed (refer to Section 10.3.1). Hormone replacement therapy will also be allowed. Acetaminophen (up to 2 g per 24-hour period) may be permitted, as necessary during the study.

13. Has been on a diet incompatible with the on-study diet, in the opinion of the investigator or designee, within the 28 days prior to the first dose and throughout the study.

14. Donation of blood or significant blood loss within 30 days prior to the first dose.

15. Plasma donation within 7 days prior to the first dose.

16. Participation in another clinical study within 28 days prior to the first dose. The 28-day window will be derived from the date of the last blood collection or dosing, whichever is later, in the previous study to Day 1 of Period 1 of the current study.

### 10.3.3 Early Termination of Subjects from the Study

Subjects are free to withdraw from the study at any time for any reason.

In addition, subjects may be withdrawn from the study by the investigator or designee for the following reasons:

- AEs.
- Difficulties in blood collection.

A subject may be withdrawn by the investigator (or designee) or the Sponsor if enrollment into the study is inappropriate, the study plan is violated, or for administrative and/or other safety reasons.

If a subject vomits within 5 hours after dosing, i.e., a period equal to two times the median tmax of MMF after administration of the reference product, he/she may be withdrawn from the study.

The clinical report will include reasons for subject withdrawals as well as details relevant to the subject's withdrawal.

## 10.4 Study Restrictions

### 10.4.1 Prohibitions and Concomitant Therapy

Consumption of foods and beverages containing the following substances will be prohibited as indicated:

- Xanthines/Caffeine: 24 hours before each dose and throughout the period of sample collection;
- Alcohol: 48 hours before each dose and throughout the period of PK sample collection;
- Grapefruit/Seville orange: 48 hours before the first dose and throughout the study.

Concomitant therapies will be prohibited as listed in the exclusion criteria in Section 10.3.2. During the study, acetaminophen (up to 2 g per 24 hours) may be administered at the discretion of the investigator or designee. Acceptable birth control methods as described in Section 10.3.1 and hormone replacement therapy will be allowed.

If deviations occur, the investigator or designee will decide on a case-by-case basis whether the subject may continue participation in the study based on the time the study drug was administered and its pharmacology.

All medications taken by subjects during the study will be recorded.

### 10.4.2 Meals

Water (except water provided with each dosing) will be restricted 1 hour prior to and 1 hour after each study drug administration, but will be allowed ad libitum at all other times. Other fluids may be given as part of meals and snacks but will be restricted at all other times throughout the confinement period.

Subjects will fast overnight for at least 10 hours prior to each study drug administration and will continue to fast for 4 hours postdose.

Standard meals will be provided at approximately 4 and 9 hours postdose, and at appropriate times thereafter. Snacks will be provided at appropriate times. When confined in the CRU, subjects will be required to fast from all food and drink except water between meals and snacks.

Each meal and/or snacks served at the CRU will be standardized and will be similar in caloric content and composition and will be taken at approximately the same time in each period/day.

### 10.4.3 Activity

Subjects will remain ambulatory or seated upright for the first 4 hours following study drug administration, except when they are supine or semi-reclined for study procedures.

However, should AEs occur at any time, subjects may be placed in an appropriate position or will be permitted to lie down on their right side.

Subjects will be instructed to refrain from strenuous physical activity which could cause muscle aches or injury, including contact sports at any time from screening until completion of the study.

## 10.5 Treatments

### 10.5.1 Treatments Administered

The test product (for Treatment A) will be supplied as 95 mg MMF delayed-release capsules (Banner Life Sciences).

The reference product (for Treatment B) will be supplied as Tecfidera® 240 mg DMF delayed-release capsules (Biogen, Inc.).

All study drugs will be administered with approximately 240 mL of water following an overnight (at least 10 hours) fast.

Subjects will be instructed not to crush, split, or chew the study drugs.

Treatments A and B are described as follows:

Treatment A (Test): a single oral dose administration of 190 mg MMF (2 x 95 mg delayed-release capsules) at Hour 0 on Day 1.

Treatment B (Reference): a single oral dose administration of Tecfidera® 240 mg DMF (1 x 240 mg delayed-release capsule) at Hour 0 on Day 1.

The pharmacy at the CRU will provide each dose in individual unit dose containers for each subject and for each study period, as per the randomization scheme.

The exact clock time of dosing will be recorded.

### 10.5.2 Method of Assigning Subjects to Treatment Groups

Each subject will be assigned a unique identification number upon screening. Subjects who complete the study screening assessments and meet all the eligibility criteria will be assigned a unique randomization identification number prior to the first dose, different from the screening number, and will receive the corresponding product, per a randomization scheme generated at Celerion.

Subjects will receive each treatment on one occasion. The sequences to be used in the randomization will be AB and BA.

Space constraints at the CRU may require subjects to be divided into 2 dosing groups of approximately equal size for dosing, as needed. Within each dosing group, subjects will be randomized to receive the test and reference products in a crossover fashion based on a randomization schedule.

Discontinued subjects will not be replaced.

### 10.5.3 Blinding

This is an open-label study.

### 10.5.4 Treatment Compliance

A qualified designee will be responsible for monitoring the administration of the timed oral doses. A mouth check will be performed by the qualified designee to ensure that the subjects have swallowed the study drug in whole without chewing. Once a subject has finished the dosing water, the qualified designee will use a flashlight and a tongue depressor to check the subject's mouth. Subjects' hands will also be verified to ensure that the study drug was ingested.

# 11 STUDY PROCEDURES

The Study Events Flow Chart (Section 6) summarizes the clinical procedures to be performed at each visit. Individual clinical procedures are described in detail below. Additional evaluations/testing may be deemed necessary by the PI or designee and/or the Sponsor for reasons related to subject safety.

For this study, the blood collection for PK assessment of MMF is the critical parameter event and blood samples need to be collected as close to the exact time point as possible. However, time deviation from scheduled sampling time will not be considered as protocol deviation, as long as the actual clock time of each sample collection is documented in the CRF. All other procedures should be completed as close to the prescribed/scheduled time as possible, but can be performed prior or after the prescribed/scheduled time. The actual date and clock time for all procedures are to be documented in the CRFs.

Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

## 11.1 Screening

Within 21 days prior to the first dose, medical history and demographic data, including name, sex, age, race, ethnicity, body weight (kg), height (cm), BMI ($kg/m^2$) and history of tobacco use will be reported. Each subject will have a physical examination, vital sign measurements (heart rate, blood pressure, and temperature), 12-lead ECG, and the laboratory tests of hematological, hepatic and renal function and additional tests as noted in Section 11.2.4.

## 11.2 Safety Assessments

### 11.2.1 Physical Examination

A full physical examination (PE) will be performed at screening as per Study Events Flow Chart (Section 6). Brief PE will be performed on Day -1 of each dose period and symptom-driven PE may be performed at other times, if deemed necessary by the PI or designee.

### 11.2.2 Vital Signs

Single measurements of body temperature, blood pressure and heart rate, will be measured as outlined in the Study Events Flow Chart (Section 6). Additional vital signs may be taken at any other times, if deemed necessary.

Vital signs measurements will be performed with subjects in a seated position, except when they are supine or semi-reclined because of study procedures and/or AEs (e.g. nausea, dizziness) or if deemed necessary by the PI or designee.

Blood pressure and heart rate will be measured approximately 2 hours prior to Day 1 dosing of each period for the predose time point. When scheduled postdose, vital signs will be performed within approximately 10 minutes of the scheduled time point.

### 11.2.3 ECG Monitoring

Single 12-lead ECGs will be performed as outlined in the Study Events Flow Chart (Section 6). Additional ECGs may be taken at any other times, if deemed necessary by the PI or designee.

ECGs will be performed with subjects in a supine position. All ECG tracings will be reviewed by the PI or designee.

ECGs will be measured approximately 2 hours prior to Day 1 dosing of Period 1.

### 11.2.4 Clinical Laboratory Tests

All tests listed below will be performed as per Study Events Flow Chart (Section 6). In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the PI or designee.

**Hematology**

- Hemoglobin
- Hematocrit
- Total and differential leukocyte count
- Red blood cell count
- Platelet count

**Serum Chemistry***

- Blood Urea Nitrogen
- Bilirubin (total and direct)
- Alkaline phosphatase
- Aspartate aminotransferase
- Alanine aminotransferase
- Albumin
- Sodium
- Potassium
- Chloride
- Glucose (fasting)
- Creatinine**

**Urinalysis**

- pH
- Specific gravity
- Protein***
- Glucose
- Ketones
- Bilirubin
- Blood***
- Nitrite***
- Urobilinogen
- Leukocyte esterase***

**Additional Tests**

- HIV test
- HBsAg
- HCV
- Urine drug screen
  - Opiates
  - Opioids
  - Amphetamines
  - Barbiturates
  - Benzodiazepines
  - Cocaine
  - Cannabinoids
- Urine alcohol screen
- Serum pregnancy test (for females only)
- FSH (for postmenopausal females only)
- Urine cotinine

* Subjects are reminded to fast for at least 8 hours prior to the blood draw for fasting clinical laboratory evaluation.

** At screening, creatinine clearance will be calculated using the Cockcroft-Gault formula.

*** If urinalysis is positive for protein, blood, nitrite and/or leukocyte esterase, a microscopic examination (for red blood cells, white blood cells, bacteria, casts, and epithelial cells) will be performed.

### 11.2.5 Adverse Events

#### 11.2.5.1 Adverse Event Definition

An AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

A suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the AE.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

#### 11.2.5.2 Monitoring

Subjects will be monitored throughout confinement for adverse reactions to the study formulations and/or procedures. Prior to release, subjects will be asked how they are feeling. At the beginning of the second period subjects will be queried with an open-ended question such as: 'How have you been feeling since your last visit?'

AEs (whether serious or non-serious) and clinically significant abnormal laboratory test value(s) will be evaluated by the PI or designee and treated and/or followed up until the symptoms or value(s) return to normal, or acceptable levels, as judged by the PI or designee.

Treatment of serious adverse events (SAEs) will be performed by a physician, either at Celerion or at a nearby hospital emergency room. Where appropriate, medical test(s) and/or examination(s), will be performed to document resolution of event(s). Outcome may be classified as resolved, improved, unchanged, worse, fatal, or unknown (lost to follow-up).

#### 11.2.5.3 Reporting

All AEs that occurred during this clinical study will be recorded. The PI or designee will review each event and assess its relationship to drug treatment (likely, probably, possibly, unlikely or unrelated). Each sign or symptom reported will be graded on a 3-point severity scale (mild, moderate, or severe), and the date of onset, time of onset, and outcome of each event will be noted.

The following definitions will be used for rating the severity of AEs:

| | |
|---|---|
| Mild | The AE is easily tolerated and does not interfere with daily activity. |
| Moderate | The AE interferes with daily activity, but the subject is still able to function. Medical intervention may be considered. |
| Severe | The AE is incapacitating and requires medical intervention. |

#### 11.2.5.4 Serious Adverse Event

If any AEs are serious, as defined by the Food and Drug Administration (FDA) Code of Federal Regulations (CFR), Chapter 21, special procedures will be followed. All SAEs will be reported to the Sponsor via fax or e-mail within one working day of becoming aware of the event, whether or not the serious events are deemed drug-related. All serious event reporting will adhere to 21 CFR 312.32 for Investigational New Drugs (IND) and to the Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE, dated December 2012. The institutional review board (IRB) will be notified of the Alert Reports as per FDA regulations.

A SAE is any AE or suspected adverse reaction that in the view of either the PI (or designee) or Sponsor, results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Life-threatening is defined as an AE or suspected adverse reaction that in the view of the PI (or designee) or Sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Unexpected is defined as an AE or suspected adverse reaction that is not listed in the IB or is not listed at the specificity or severity that has been observed; or is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

If a SAE occurs to a subject on this study, contact the Sponsor personnel listed in Section 3.

### 11.3 Pharmacokinetic Assessments

#### 11.3.1 Blood Sampling and Processing

For all subjects, blood samples for the determination of MMF will be collected in prechilled blood collection tubes containing sodium fluoride/potassium oxalate as the stabilizer and anticoagulant, respectively at scheduled time points as delineated in the Study Events Flow Chart (Section 6) by direct venipuncture using a disposable sterile needle at each time of collection.

Blood collection tubes will be placed in an ice bath at least 5 minutes prior to blood collection. Immediately upon blood collection, the collection tubes will be gently inverted

8-10 times to allow mixing with the anticoagulant and the stabilizer, and will be cooled in an ice bath and centrifuged (approximately at 2056 x gravity for 7 minutes) under refrigeration at a temperature of approximately 4°C as soon as possible and no later than 60 minutes upon collection. Plasma samples will be divided into 4 aliquots and stored in suitably labeled polypropylene tubes which are prechilled and contain pre-aliquoted an appropriate volume (100 µL per 1 mL of plasma) of the 10% (v/v) phosphoric acid solution in each tube as a stabilizer. The storage tubes will be labeled, at a minimum, with Sponsor company, protocol number, subject number, sample matrix, study period, study day, scheduled sample time and tube number (eg., #1, #2, #3, #4). Tubes will be stored in an upright position in a non-self-defrosting freezer with the temperature maintained at approximately -70°C or lower until shipment to the designated bioanalytical laboratory where samples will be stored at approximately -70°C or lower. Samples should be placed into the freezer within 90 minutes of blood collection.

At the end of the study, the first aliquot (Aliquot #1) of each plasma sample will be shipped together to the Sponsor's designated bioanalytical laboratory; while the second aliquot (Aliquot #2) will be sent after receipt in good condition of the previous shipment. The other aliquots of each sample will be retained at the CRU until further instruction for shipment.

Additional instruction for blood sampling, collection, processing, and sample shipment will be provided separately.

### 11.3.2 Analytical Method

Samples will be analyzed for plasma MMF using validated bioanalytical methods. Samples from subjects to be assayed are specified in Section 12.2.2.

## 11.4 Blood Volume Drawn for Study Assessments

### Table 1: Blood Volume during the Study

| Sample Type | Number of Time Points | Approximate Volume per Time Point * (mL) | Approximate Sample Volume Over Course of Study (mL) |
|---|---|---|---|
| Screening laboratory safety tests (including hematology, serum chemistry, and serology), FSH (for postmenopausal female subjects only) and serum pregnancy (for female subjects only). | 1 | 12.5 | 12.5 |
| On-study hematology and serum chemistry (this includes serum pregnancy for female subjects only when scheduled at the same time) | 2 | 12.5 | 25 |
| Blood for MMF | 44 | 10 | 440 |
| | | Total Blood Volume (mL)→ | 477.5 ** |

* Represents the largest collection tube that may be used for this (a smaller tube may be used).

** If additional safety or PK analysis is necessary or if larger collection tubes are required to obtain sufficient plasma/serum for analysis, additional blood may be obtained (up to a maximum of 90 mL).

# 12 DATA ANALYSIS

Data will be handled and processed according to Celerion Standard Operating Procedures, which are written based on the principles of GCP.

## 12.1 Pharmacokinetic Parameters

PK analysis of plasma concentration vs. time data of MMF will be performed using noncompartmental methods with the following parameters calculated as appropriate or data permitting:

| | |
|---|---|
| AUC0-t: | The area under the concentration-time curve, from time 0 (dosing time) to the last time point (tlast) with measureable drug concentration, as calculated by the linear trapezoidal method. |
| AUC0-inf: | The area under the concentration-time curve from time 0 (dosing time) extrapolated to infinity. AUC0-inf is calculated as the sum of AUC0-t plus the ratio of the last measurable drug concentration to the apparent terminal first-order decay rate constant. |
| AUC%extrap: | Percent of AUC0-inf extrapolated from the last time point with measurable drug concentration to infinity calculated as (1 - AUC0-t/AUC0-inf)*100. |
| Cmax: | Maximum observed drug concentration. |
| tmax: | Time to reach Cmax. If the maximum value occurs at more than one time point, tmax is defined as the first time point with this value. |
| Kel: | Apparent terminal first-order decay rate constant calculated from a semi-log plot of the plasma concentration-time curve. The parameter will be calculated by linear least-squares regression analysis using at least 3 appropriate time points in the terminal log-linear phase. |
| t½: | Apparent plasma half-life which will be calculated as 0.693/Kel. |

No value for Kel, AUC0-inf, AUC%extrap, or t½ will be reported for cases that do not exhibit an apparent terminal log-linear phase in the concentration-time profile. No PK parameters will be calculated for subjects with 3 or fewer consecutive time points with detectable concentrations throughout the collection period.

## 12.2 Statistical Methods

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP). The SAP will be prepared by Celerion and agreed upon with the Sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoints definition and/or its analysis will also be reflected in a SAP amendment. Additional statistical analyses other than those described in this section may be performed if deemed appropriate and will be presented in the SAP and clinical study report.

### 12.2.1 Determination of Sample Size

The sample size was calculated [5] using a power of at least 95% and an alpha error of 5%. The power was defined as the probability of having a 90% CI to a Test/Reference ratio within the acceptance criteria of 80.00 - 125.00%. A true ratio between 95 - 105% was assumed and an intra-subject CV of 24% was used. A total of 50 subjects will be dosed. This includes 6 additional subjects to account for possible dropouts or non-evaluable data.

### 12.2.2 Subjects to Analyze

PK Population: Plasma samples from all subjects will be assayed even if the subjects do not complete the study. All subjects who comply sufficiently with the protocol and display an evaluable PK profile (e.g., exposure to treatment, availability and validity of measurements, and absence of major protocol violations) will be included in the PK analyses to determine PK parameters of MMF. Subjects who vomited within 5 hours after drug dosing may be excluded from the PK analyses.

Statistical Population: Statistical analysis will be performed on all subjects contributing to PK parameters of MFF (Cmax, AUC0-inf, and AUC0-t). However, BE assessment will be primarily based on PK parameter data from subjects who complete the study or have sufficient data for a pairwise comparison, i.e., from both treatments.

Safety Population: All subjects who received at least one dose of the study drug will be included in the safety evaluations.

### 12.2.3 Descriptive Statistics

Values will be calculated for the plasma concentrations and the PK parameters listed in Section 12.1 using appropriate summary statistics to be fully outlined in the SAP.

### 12.2.4 Statistical Analysis

An ANOVA will be performed on the ln-transformed AUC0-t, AUC0-inf, and Cmax using SAS® Proc Mixed. The ANOVA model will include sequence, treatment, and period as fixed effects, and subject nested within sequence as a random effect. Each ANOVA will include calculation of least-squares means (LSM) of the ln-transformed parameter as well as the LSM difference between treatments.

Ratios of geometric LSM (GLSM) will be calculated using the exponentiation of the difference between treatment LSM from the analyses on the ln-transformed AUC0-t, AUC0-inf, and Cmax. These ratios will be expressed as a percentage, test relative to the reference (Treatment A vs. Treatment B).

Consistent with the two one-sided test, [6] 90% CIs for the GLSM ratios will be derived by exponentiation of the CIs obtained for the LSM difference between treatments resulting from the analyses on the ln-transformed AUC0-t, AUC0-inf, and Cmax. The CIs will be expressed as a percentage, test relative to the reference (Treatment A vs. Treatment B).

Bioequivalence criteria will be met if the 90% CIs for the ratios of GLSMs of Cmax and AUC0-inf of MMF of the Test (Treatment A) to the Reference (Treatment B) fall within the limit of 80.00 and 125.00%.

Time to maximal drug concentration, tmax, will also be analyzed without transformation using a non-parametric method (Wilcoxon test). This analysis will only be performed for information purpose, not for BE assessment.

Additional details of statistical analysis methods will be included in the SAP.

### 12.3 Safety Evaluation

All safety data will be populated in the individual CRFs. All safety data will be listed by subjects.

Dosing dates and times will be listed by subject.

AEs will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA®) available at Celerion and summarized by treatment for the number of subjects reporting the TEAE and the number of TEAEs reported. A by-subject AE data listing including verbatim term, coded term, treatment, severity, and relationship to treatment will be provided.

Safety data including vital signs assessments and clinical laboratory evaluations will be summarized by treatment and point of time of collection.

Descriptive statistics using appropriate summary statistics will be calculated for quantitative safety data as well as for the difference to baseline, when appropriate. In addition, a shift table describing out of normal range shifts will be provided for clinical laboratory results.

Concomitant medications will be listed by subject and coded using the most current version of WHO drug dictionary available at Celerion. Medical history will be listed by subject.

# 13 STUDY ADMINISTRATION

## 13.1 Ethics

### 13.1.1 Institutional Review Board

This protocol will be reviewed by the Chesapeake Research Review, Inc. IRB, and the study will not start until the IRB has approved the protocol or a modification thereof. The IRB is constituted and operates in accordance with the principles and requirements described in the US Code of Federal Regulations (21 CFR Part 56). The IRB is compliant to International Conference on Harmonisation (ICH) guidelines, and may be reached at:

Chesapeake IRB
6940 Columbia Gateway Drive, Suite 110
Columbia, Maryland 21046, USA
Tel.: +1 410 884-2900

### 13.1.2 Ethical Conduct of the Study

This research will be carried out in accordance with the protocol, US Code of Federal Regulations, 21 CFR Parts 50, 56, and 312, the ethical principles set forth in the Declaration of Helsinki, GCP, and the ICH harmonized tripartite guideline regarding GCP (E6 Consolidated Guidance, April 1996).

### 13.1.3 Subject Information and Consent

The purpose of the study, the procedures to be carried out and the potential hazards will be described to the subjects in non-technical terms. Subjects will be required to read, sign and date an ICF summarizing the discussion prior to screening, and will be assured that they may withdraw from the study at any time without jeopardizing their medical care.

Subjects will be given a copy of their signed ICF.

## 13.2 Termination of the Study

Celerion reserves the right to terminate the study in the interest of subject welfare.

## 13.3 Data Quality Assurance

Standard operating procedures are available for all activities performed at Celerion relevant to the quality of this study. Designated personnel of Celerion will be responsible for implementing and maintaining quality assurance (QA) and quality control systems to ensure that the study is conducted, and that data are generated, documented and reported in compliance with the study protocol, GCP and Good Laboratory Practice requirements as well as applicable regulatory requirements and local laws, rules and regulations relating to the conduct of the clinical study.

The Clinical Study Report will be audited by the QA department and the QA audit certificate will be included in the study report.

All clinical data will undergo a 100% quality control check prior to clinical database lock. Edit checks are then performed for appropriate databases as a validation routine using SAS® or comparable statistical program to check for missing data, data inconsistencies, data ranges, etc. Corrections are made prior to database lock.

### 13.4 Direct Access to Source Data/Documents

Celerion will ensure that the Sponsor, IRB and inspection by domestic and foreign regulatory authorities will have direct access to all study-related sites, source data/documents, and reports for the purpose of monitoring and auditing (ICH[E6] 5.1.2 & 6.10). In the event that other study-related monitoring should be done by other parties, they will be required to sign a confidentiality agreement prior to any monitoring and auditing.

### 13.5 Drug Supplies, Packaging and Labeling

The Sponsor will supply sufficient quantities of the study formulations to allow completion of this study. The lot numbers and expiration dates (where available) of the study drugs supplied will be recorded in the final report.

Records will be made of the receipt and dispensing of the study drugs supplied. At the conclusion of the study, any unused study drugs will be retained by Celerion, returned to the Sponsor or designee, or destroyed, as per Sponsor instructions. If no supplies remain, this fact will be documented in the pharmacy product accountability records.

### 13.6 Data Handling and Record Keeping

Celerion standard CRFs will be supplied. CRFs are printed off directly from the database. Each CRF is reviewed and signed by the PI.

All raw data generated in connection with this study, together with the original copy of the final report, will be retained by Celerion until at least 5 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 5 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the Sponsor to inform the PI/Institution as to when these documents no longer need to be retained.

### 13.7 Report Format

Per the ICH Harmonized Tripartite Guideline (Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use M4 and the ICH M2 Expert Working Group), a full final report will be written per the ICH E3 Guideline (Structure and Content of Clinical Study Reports).

### 13.8 Publication Policy

All unpublished information given to Celerion by the Sponsor shall not be published or disclosed to a third party without the prior written consent of the Sponsor.

The data generated by this study are considered confidential information and the property of the Sponsor. This confidential information may be published only in collaboration with participating personnel from the Sponsor or upon Sponsor's written consent to publish the article.

## 14 REFERENCES

1 Tecfidera® (240 mg dimethyl fumarate) delayed-release capsules, full prescribing information (electronic monograph) published on the FDA website (document revised: Feb/2015). Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/204063s014lbl.pdf, accessed on: 17Oct2016.

2 Monomethyl fumarate (200 mg and 95 mg delayed-release capsules). Investigator's Brochure. Banner Life Sciences. 2016.

3 Food and Drug Administration: Center for Drug Evaluation and Research (CDER). Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations (March 2003). Available at: http://www.fda.gov/ohrms/dockets/ac/03/briefing/3995B1_07_GFI-BioAvail-BioEquiv.pdf, accessed on: 17Oct2016.

4 Food and Drug Administration: Center for Drug Evaluation and Research (CDER). Guidance for Industry: Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs - General Considerations (Draft March 2014). Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM389370.pdf, accessed on: 17Oct2016.

5 Hauschke D, Steinijans VW, Diletti E. and Burke M. Sample size determination for bioequivalence assessment using a multiplicative model. J Pharmacokinet Biopharm 1992;20(5):557-561.

6 Schuirmann DJ. A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. J Pharmacokinet Biopharm 1987;15: 657-680.